TÜBİTAK

Turkish Journal of Biology

http://journals.tubitak.gov.tr/biology/

Review Article

Turk J Biol
(2016) 40: 333-352
© TÜBİTAK
doi:10.3906/biy-1507-18

# A matter of regeneration and repair: caspases as the key molecules

**Şehnaz BOLKENT*, Füsün ÖZTAY, Selda GEZGİNCİ OKTAYOĞLU, Serap SANCAR BAŞ, Ayşe KARATUĞ**
Department of Biology, Faculty of Science, İstanbul University, Vezneciler, İstanbul, Turkey

**Received:** 03.07.2015 • **Accepted/Published Online:** 09.10.2015 • **Final Version:** 23.02.2016

**Abstract:** Researchers have been focused on understanding the pathogenesis of human diseases. They have been working to find the roles of caspases in the balance between apoptosis, autophagy, pyroptosis, and necroptosis, and also in the regeneration of damaged tissue. At this point, besides their death-inducing roles, new findings indicate the role of caspases in proliferation for maintaining the viability of cells in response to signals from apoptotic cells. Recently, determining cell fate has also been identified among other functions of caspases. Findings indicate that caspases direct cellular pathways to cell differentiation by suppressing stem cell self-renewal. The common opinion about the related mechanism is that low and transient caspase activation leads to terminal differentiation by affecting the expression of key genes related to differentiation. Moreover, caspases are essential proteases in the regulation and modulation of the repair process. In repair, they have roles in apoptosis, release of inflammatory cytokines and chemokines, promotion of cell migration, and immune cell infiltration. However, paracrine signaling through caspase activation leads to cell proliferation after cancer therapy and causes tumor relapse, which complicates the current therapy. In this scope, we have reviewed the main mechanisms of pathological, regenerative, and restorative effects of caspases.

**Key words:** Caspases, cell death, proliferation, stem cell, self-renewal, differentiation, regeneration, repair, tumor relapse, aging

## 1. Introduction

Caspases (cysteine-aspartic proteases) are intracellular proteolytic enzymes that have well-defined roles in apoptosis, but little is known about their nonapoptotic roles in different cell death types such as pyroptosis, necroptosis, autophagy, and mitotic catastrophe (Kroemer et al., 2009; McIlwain et al., 2013; Shalini et al., 2015) (Figure 1). Caspases are divided into three groups in terms of apoptosis and inflammation, namely inflammatory caspases, initiator caspases, and effector caspases. Caspases are important regulatory molecules providing tissue homeostasis by regulating cell death and inflammation (Lavrik et al., 2005).

In multicellular organisms, caspases are found in the cytoplasm of cells as inactive monomeric zymogenic precursors, known as procaspases; then they dimerize as a reaction to cell death stimulants and are activated with autoproteolytic cleavage (McIlwain et al., 2013; Connolly et al., 2014). After this autocatalytic cleavage, mature caspases become proteolytically active heterotetramers, containing two small and two large subdomains. These initiator caspases cause activation by the cleavage of downstream effector caspases, which accelerate cell breakdown by targeting many important cellular proteins, including the proteins related to signal transduction pathways and DNA repair, and other structural proteins. Active caspases cleave several substrates that take part in apoptosis and inflammation in a specific manner. The cascade of activated effector caspases is different in intrinsic and extrinsic pathways. Defects occurring in these caspases might contribute to autoimmune diseases, degenerative diseases, type 2 diabetes, stroke, cancer, and some neurological disorders (Lavrik et al., 2005; McIlwain et al., 2013; Shalini et al., 2015).

The function of caspases cannot be limited to cell death. Many studies have suggested that active caspases are associated with cell and tissue differentiation, compensatory proliferation, cell migration, neural development, immune response, inflammation, scar remediation, synaptic plasticity, stem cells and self-renewal, DNA damage, and aging in many biological events associated with restoring and regeneration, and even with tumor development and metastasis (Kuranaga and Miura, 2007; Li and Yuan, 2008; Fuchs and Steller, 2011; Miura, 2012; Shalini et al., 2015). The studies mentioned above have shown that caspases mediate apoptosis and other nonapoptotic cell deaths in addition to various biological processes, but especially in the latter case, the molecular mechanisms are not fully known.

* Correspondence: sbolkent@istanbul.edu.tr

## 2. Caspases and cell deaths

Cell death is an important process, providing tissue homeostasis by recycling the cellular components that stimulate growth and differentiation, and by killing the unwanted and damaged cells. The role of caspases in cell death during the growth of *Caenorhabditis elegans* has been well known since the discovery of *ced-3*, which is the executioner of cell death (Ellis and Horvitz, 1986). Due to the discrepancies in the renomenclature of caspases, 18 caspases are known as of today. Caspases controlling cell death are caspase-2, -3, -6, -7, -8, -9, and -10, being apoptotic caspases, while caspases related to inflammation are inflammatory caspase-1, -4, -5, -11, and -12. The roles of other caspases are not yet clear. Apoptotic caspases are again divided into two groups in terms of the presence or absence of specific protein interaction domains through the N-terminal, respectively initiator caspases (caspase-2, -8, -9, and -10) and executioner caspases (caspase-3, -6, and -7) (McIlwain et al., 2013; Connolly et al., 2014; Shalini et al., 2015) (Figure 1).

### 2.1. Caspases in apoptotic cell death pathways

Activation of initiator caspases in apoptotic cell death progresses through two pathways, one of which is intrinsic, regulated by mitochondrial cytochrome *c* and Bcl-2, while the other, namely the extrinsic pathway, is regulated by cell surface receptors (Shalini et al., 2015).

#### 2.1.1. Intrinsic pathway (mitochondrial apoptosis)

Several cellular stresses such as oxidative stress and DNA damage, an increase in cytosolic calcium concentration, and accumulation of unfolded proteins in endoplasmic reticulum cause the activation of the Bcl-2 protein family, which also includes proapoptotic effectors like p53 and Bax/Bak, and this activation causes the mitochondrial outer membrane permeabilization and mitochondrial permeability transition, eventually yielding the release of cytochrome *c* (Galluzzi et al., 2012; Shalini et al., 2015). Apoptosome, consisting of apoptotic protease-activating factor-1 (Apaf-1), cytochrome *c*, adenosine triphosphate

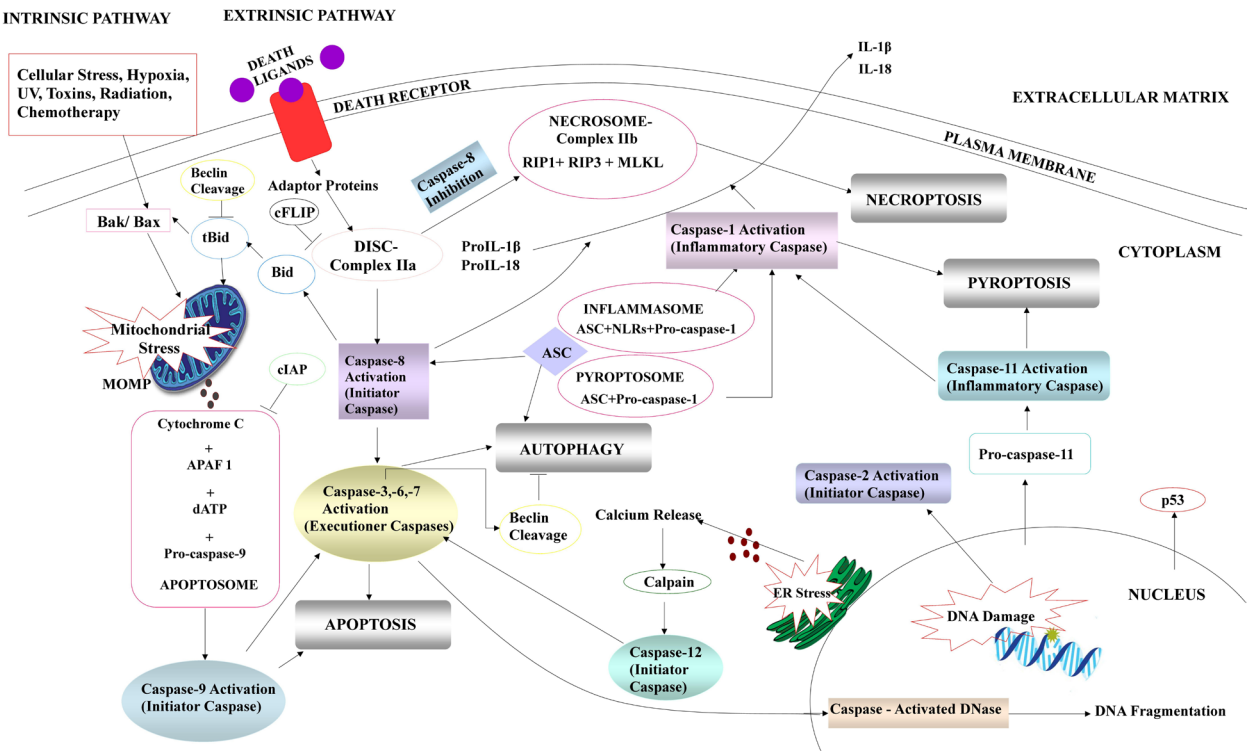


**Figure 1.** Molecular pathways associated with caspases in apoptotic and nonapoptotic cell deaths, such as pyroptosis, necroptosis, and autophagy. In the intrinsic pathway of apoptosis: cytochrome c release from mitochondria and apoptosome formation, then caspase-9 activation. In the extrinsic pathway of apoptosis: binding death ligand to the receptor, DISC formation, caspase-8 activation, and then caspase-3, -6, and -7 activation. In pyroptosis, inflammasome formation, and caspase-1 and -11 activation. In necroptosis, caspase-8 inhibition and necrosome formation. Caspase-1- and -8-mediated pro-IL-1β and pro-IL-18 processing and IL-1β and IL-18 maturation. Cleavage of autophagic proteins such as Beclin and inhibition of autophagy. APAF-1: Apoptotic protease-activating factor-1; Bak: Bcl-2 antagonist or killer; Bax: Bcl-2-associated X protein; Bid: BH3-interacting domain death agonist; Complex IIa: TRADD, procaspase-8, FADD, and $cFLIP_L$; Complex IIb: stabilized RIP1 and RIP3 associate in microfilament-like complexes; cFLIP: cellular FADD-like IL-1β-converting enzyme; DISC: death-inducing signaling complex; IAPs: inhibitors of apoptosis proteins; MLKL: mixed lineage kinase domain-like; MOMP: mitochondrial outer membrane permeabilization; RIP: receptor-interacting protein; tBid: proteolytically activated Bid.

(ATP), and caspase-9, is activated and then procaspase-9 is cleaved into active caspase-9. Subsequently, active caspase-9 cleaves the effector caspases such as procaspase-3, -6, and -7 to yield active caspase-3, -6, and -7, and thus the active caspases stimulate cell death (McIlwain et al., 2013; Shalini et al., 2015). Following the induced oxidative stress and DNA damage, caspase-2 is also activated and cleaves Bid, and then stimulates mitochondrial outer membrane permeabilization (Shalini et al., 2015) (Figure 1).

**2.1.2. Extrinsic pathway (receptor-mediated apoptosis)**

This pathway is activated by binding of the ligand to the death receptor on the cell surface. Based on ligands such as tumor necrosis factor alpha (TNF-α), Fas ligand (FasL), and TNF-related apoptosis-inducing ligand (TRAIL), different complexes are produced. Adapter proteins interact with cell death domains like the Fas-associated death domain/TNF receptor-associated death domain (FADD/TRADD) (Lavrik et al., 2005; McIlwain et al., 2013, Shalini et al., 2015). TNF stimulates TNF receptor-1, which constitutes of cellular inhibitor of apoptosis protein (cIAP), TNF receptor-associated factor, and receptor-interacting protein (RIP) 1 and forms a large complex known as the TRADD-dependent first complex. This complex is decomposed with the extraction of polyubiquitin chains on RIP1. A death-inducing signaling complex (DISC) then binds FADD and procaspase-8. Apoptosis is stimulated by activating the caspase-8 second complex. Cellular FLICE-like inhibitor protein ($cFLIP_L$) interacts by binding with FADD and caspase-8. Subsequently, caspase-8 cleaves RIP1 and RIP3, and then apoptosis starts, whereas inhibition of caspase-8 prevents apoptosis and initiates necroptosis (Shalini et al., 2015). On the other hand, active caspase-8 either directly initiates apoptosis and indirectly activates executioner caspases (caspase-3, -6, and -7), or stimulates the mitochondrial/intrinsic apoptotic pathway by cleavage of Bid to release cytochrome *c* (McIlwain et al, 2013, Shalini et al., 2015).

Mitotic catastrophe is a special example of cell death observed during mitosis in cells with accumulated DNA damage induced by various physical and chemical agents. Activation of caspase-2 and release of cytochrome *c* occur. The cells reach the G1 phase of the cell cycle and then die or exit mitosis and undergo senescence (Galluzzi et al., 2012) (Figure 1).

**2.2. Caspases in nonapoptotic cell death pathways**

Caspases play important roles in necroptosis, pyroptosis, and autophagy, all of which are nonapoptotic cell deaths.

**2.2.1. Caspases in the necroptotic cell death pathway**

Necrosis is a nonprogrammed cell death occurring with several factors released from dead cells, with disintegration of the cell membrane after cell damage. As a result of inhibition of apoptosis- and autophagy-related specific proteins, this type of cell death can be converted into necrosis (Golstein and Kroemer, 2006; Kroemer et al., 2009). However, necroptosis is a programmed type of cell death mechanism that occurs in response to some inflammatory diseases when there is no or blocked caspase activity (Vercammen et al., 1998; Berghe et al., 2014). This type of cell death was first observed in L929 cells stimulated with TNF-α in the presence of caspase inhibitor, and thus it was demonstrated that low levels of caspase activity have a protective effect. Consequently, the possibility of using caspase inhibitors for the therapy of several diseases has been raised. The inhibition of caspase activation by different inhibitors blocks apoptotic cell death, sensitizes cells to necrotic cell death, and induces necroptosis (Vercammen et al., 1998; Nikoletopoulou et al., 2013). The role of caspase inhibitors in the therapy of various diseases will be revealed in greater detail when the molecular mechanisms of regulated necroptosis and interconnected signal pathways are examined.

Necroptotic cell death was confirmed with the findings of proteins like RIP1 or a mitochondrial apoptosis-inducing factor (Delavallée et al., 2011). Necroptotic cells are defined with a necrotic morphology, namely disintegration in the cell membrane, swelling in the organelles, and increase in the cell volume (Vandenabeele et al., 2010). When caspase activity is blocked, in some conditions, RIP1, FADD, and $cFLIP_L$-caspase-8 heterodimer form "ripoptosome" (a multiprotein complex) followed by genotoxic stress, and the cell goes into apoptosis. However, when caspase-8 activity is inhibited with $cFLIP_S$, RIP1 and RIP3 are stabilized and phosphorylated. Then the mixed lineage kinase domain-like protein is phosphorylated and necroptosis begins with the formation of "necrosome" (Galluzzi et al., 2012; Shalini et al., 2015) (Figure 1).

Receptor interacting protein kinase 1 and 2 in TNF-, FasL-, and TRAIL-mediated necroptosis are important mediators. TRAIL induced apoptosis at pH 7.4 and at lower ATP levels, but TRAIL induced necroptosis at pH 6.5 and in elevated ATP depletion. Use of RIP kinase inhibitors such as necrostatin-1 or geldanamycin causes a switch from necroptosis to apoptosis at acidic pH and with partial ATP saturation (Jouan-Lanhouet et al., 2012). When cell death receptors are stimulated, cell death progresses through alternative cell death pathways (Shalini et al., 2015) (Figure 1).

**2.2.2. Caspases in the pyroptotic cell death pathway**

Pyroptosis is a programmed type of cell death occurring after the activation of inflammatory caspases (caspase-1 and mouse caspase-11) seen first in macrophages due to an infection (Monack et al., 1996; Fink and Cookson, 2005; Aachoui et al., 2013; Shalini et al., 2015). This is probably caused by the formation of membrane pores, having osmotic water flow into the cell, and the cell swells and lysis occurs (Labbé and Saleh, 2011; Aachoui et al., 2013).

In response to bacterial and viral infections or when subjected to bacterial toxins, specific pathogen- or danger-related molecular patterns cause the formation of the inflammasome complex (Bergsbaken et al., 2009). Caspase-1 activation is initiated by different inflammasome complexes (Labbé and Saleh, 2011; Shalini et al., 2015). Activated caspase-1 stimulates proinflammatory cytokines like interleukin (IL)-1 beta (β) and IL-18, transforming them into their mature forms (Fink and Cookson, 2005; Shalini et al., 2015). After being subjected to pathogens, toll-like receptors stimulate the transcription of nuclear factor kappa B ($NF_KB$)-mediated IL-1β and IL-18 (Shalini et al., 2015) (Figure 1).

In another pathway, followed by viral infection, interferon-β promoter stimulator 1 is added to the *retinoic acid-inducible* gene complex with the activation of retinoic acid-like receptors, and then a greater complex is formed by including caspase-8 and the DISC complex (FADD, TRADD, and ubiquitin-conjugated RIP1). Then ubiquitin-conjugated RIP1 increases the phosphorylation of interferon regulatory factor 3. RIP1 is cleaved by activated caspase-8 and inhibits interferon regulatory factor 3 and NFκB, and it suppresses the inflammatory response (Labbé and Saleh, 2011; Denes et al., 2012; Shalini et al., 2015).

Caspase-11 is activated with a different inflammasome rather than the one activating caspase-1, as a result of being subjected to toxins or bacteria for a prolonged time. Activated caspase-11 uses the noncanonical inflammasome pathway and causes pyroptosis by activating caspase-1 (Viganò and Mortellaro, 2013). The aforementioned caspase-1, -4, -5, -11, and -12 are known as inflammatory caspases (Martinon and Tschopp, 2007; Shi et al., 2014; Sollberger et al., 2014) (Figure 1).

**2.2.3. Caspases in the autophagic cell death pathway**

Autophagy is a cell death mechanism, having cytoprotective and homeostatic functions, observed in growth and providing survival in response to stress. There is notable crosstalk among autophagy and apoptosis (Gozuacik et al., 2008; Shalini et al., 2015). In addition, autophagy can decrease the inflammatory response by regulating pyroptosis, which is a caspase-1-mediated cell death mechanism (some caspases like caspase-3 mediate the cleavage of important autophagic proteins, like Beclin) and it reduces autophagy in an indirect manner and promotes apoptosis. Caspase-2, -3, -6, -7, -8, and -10 have an antiautophagic effect that inhibits autophagy, while caspase-3 and caspase-9 have proautophagic effects (Norman et al., 2010; Oral et al., 2012; Tiwari et al., 2014; Wu et al., 2014; Shalini et al., 2015). The roles of the protein–protein interactions between caspases and some proteins such as Atg in caspase-mediated autophagy-apoptosis crosstalk are still unclear (Figure 1).

**3. Caspases in cell proliferation**

Regeneration occurs in various circumstances in response to damage in the tissue. These are such circumstances as wound healing, differentiation, and a high degree of proliferation in cells with the ability of growing and regenerating in a certain part of the body or the organs (Gurtner et al., 2008). It was revealed that apoptosis is a driving force behind regeneration. The signals of apoptotic cells induce proliferation that occurs during regeneration. This is defined as apoptosis-induced compensatory proliferation (Bergmann and Steller, 2010).

While caspases are principally associated with apoptosis, a portion of these enzymes affect proliferation. In the case of stress or damage, cells going through apoptosis may induce the proliferation of the adjacent cells. Experiments showing this condition were first conducted in *Drosophila* (Pérez-Garijo et al., 2004; Ryoo et al., 2004). Due to the fact that dying cells were quickly removed from the environment through phagocytosis, how these cells affected the compensatory proliferation was not clear. For this reason, p35 inhibiting the effector caspases in the experiments carried out in *Drosophila* was used in order to block cell death (Huh et al., 2004; Pérez-Garijo et al., 2004). Although the apoptotic pathway is active, p35 expression prevents the advancement of cell death and provides emission of the signals for compensatory proliferation by keeping cells alive. This experiment, which was carried out using p35, ensured the definition of the components in the apoptotic pathway associated with compensatory proliferation. In the case of the loss of the gene copy of *Dronc*, which is the initiator caspase in *Drosophila* that is similar to caspase-9, compensatory proliferation was suppressed, although the effector caspases were active. *Drosophila* ICE (DrICE) and death caspase-1 (Dcp-1) are caspases in *Drosophila* that are similar to caspase-3, which can play a role in apoptosis and compensatory proliferation. For this reason, there are two different cases in the compensatory proliferation induced by apoptosis. One of them is related to Dronc, which is the initiator caspase, and the other is related to DrICE and Dcp-1, which are effector caspases (Fan and Bergmann, 2008a).

There are two different types of mitogens activated by caspases in order to induce the compensatory proliferation. The first one is *decapentaplegic* (*Dpp*) in *Drosophila*, the homolog of transforming growth factor (TGF)-β, and the other one is the segment polarity gene *wingless* (*Wg*) in *Drosophila*, the homolog of Wnt (Pérez-Garijo et al., 2004; Ryoo et al., 2004). Despite this, the effect of these mitogens and signal pathways on compensatory proliferation is not completely understood. Sonic Hedgehog (Shh) signals are necessary in apoptosis-induced compensatory proliferation for the differentiation of *Drosophila* retina. Postmitotic photoreceptor neurons release Shh in response

to stress and then proliferation of the adjacent cells is induced (Fan and Bergmann, 2008b). Dronc and p53 are necessary in Wg, Dpp, and *c*-Jun N-terminal kinase (JNK) pathways, but Shh activation occurs downstream of DrICE and Dcp-1 (Fuchs and Steller, 2011). In addition to Wnt and TGF-β, JNK signal activity was also shown in mammalian liver regeneration (Maeda et al., 2005; Sakurai et al., 2006; Zhong et al., 2006). In kidney tissue, it was shown that a proliferative response occurs in living cells for the regeneration of the damaged tubules. Supportive data were obtained by Gezginci-Oktayoglu et al. (2008). They showed that tubular epithelial cell apoptosis and proliferation increase in D-galactosamine/TNF-α-induced kidney injury by caspase-3 in order to induce compensatory proliferation.

Notch and Janus kinases-signal transducers and activators of transcription (JAK-STAT) signal pathways were associated with proliferation, which can be induced by apoptosis (Moberg et al., 2005; Thompson et al., 2005; Vaccari and Bilder, 2005; Herz et al., 2006). Mutations in *ubiquitin-like modifier activating enzyme 1*, which catalyzes the activation stage in the ubiquitin conjugation pathway, induce apoptosis directly and tissue growth indirectly. The activation of Notch and JAK-STAT signals in *ubiquitin-like modifier activating enzyme 1* mutant cells shows that this is necessary for indirect tissue growth (Pfleger et al., 2007; Lee et al., 2008). JNK signals, which are important for compensatory proliferation and wound healing (Ryoo et al., 2004; Bosch et al., 2005), are activated through compensatory proliferation in the development of wing disks in *Drosophila*. Initial studies indicated that JNK acts downstream of Dronc in p35-expressing apoptotic cells in order to regulate the expression of mitogens (Ryoo et al., 2004). In subsequent studies, it was found that JNK induces compensatory proliferation in apoptotic cells expressing p35 independently from the apoptotic program. The mutual expression of Dronc and p35 activates JNK and induces tissue growth. In this way, it imitates compensatory proliferation (Kondo et al., 2006; Pérez-Garijo et al., 2009). How JNK regulates *Wg* or *Dpp* is not known.

Caspases are also effective in nonapoptotic conditions, playing a part in cell proliferation (Kuranaga and Miura, 2007; Yi and Yuan, 2009). The relationship between caspases and proliferation was revealed as a result of studies carried out with regard to caspases-3, -6, -7, and -8. It was shown that proliferation increases in vivo in caspase-$3^{-/-}$ B cells and hyperproliferation occurs following the mitogenic warning in vitro (Woo et al., 2003). Caspase-3 has a proliferative effect in forebrain cells and keratinocytes (Yan et al., 2001; Okuyama et al., 2004). The role of caspase-3 and -7 in the proliferation of stem and progenitor cells was investigated by the injection of caspase-$3^{-/-}$ or caspase-$7^{-/-}$ epidermal keratinocyte progenitor cells into the back feet of fatally irradiated mice. It was indicated that fatally irradiated caspase-$3^{-/-}$ and caspase-$7^{-/-}$ fibroblasts were less effective at stem and progenitor cell proliferation compared to wild-type fibroblasts. Proliferation is the lowest in the caspase-$3^{-/-}$ model. It is said that this type of caspase has an important role in this advancement. Defects were shown in wound healing and cell proliferation in caspase-$3^{-/-}$ and -$7^{-/-}$ mice. Caspase-3 and -7 are also important in partial hepatectomy models for the improvement in mice. Regenerative cell proliferation in caspase-$3^{-/-}$ and -$7^{-/-}$ mice decreased by approximately 50% and the studies carried out showed that there are executioner caspases in cell proliferation during wound healing and cell regeneration (Li et al., 2010).

It was shown that caspase-8 pushes forward the growth in T cells, and caspase-6 and -8 positively regulate the proliferation of B cells (Lens et al., 2002; Olson et al., 2003; Beisner et al., 2005). Caspase-8 has also enhanced proliferation in natural killer cells. The proliferative role of caspase-8 was shown in immune cells (Chun et al., 2002; Salmena et al., 2003; Beisner et al., 2005; Su et al., 2005). Caspase-8 may initiate apoptosis, but it also plays a part in the regulation of NFκB activation and lymphocyte proliferation. Whether caspase-8 activation is apoptotic or nonapoptotic is defined via its activation level. Caspase-8 transduction does not occur and its activation falls in proliferating cells (Su et al., 2005). Nevertheless, caspase-8 processes and powerful activation are observed during FasL-induced apoptosis (Peter and Krammer, 2003). The c-$FLIP_L$, which is a caspase-8-like molecule deprived of caspase-8 activity, is important for the regulation of caspase-8 activation during DISC formation (Tschopp et al., 1998; Micheau et al., 2002). Being more effective than the homodimer mutually created by caspase-8 (Boatright et al., 2004), c-$FLIP_L$ creates a heterodimeric form together with caspase-8 (Chang et al., 2002; Micheau et al., 2002; Boatright et al., 2004). For this reason, the activation of procaspase-8 increases in cases of low concentration of c-$FLIP_L$. At this point, apoptosis-independent events such as NFκB activation and cell proliferation may follow each other (Kataoka and Tschopp, 2004; Dohrman et al., 2005). In cases of high concentrations of c-$FLIP_L$, the interaction of caspase-8 and DISC is blocked and caspase-8 transduction is prevented; hence, the initiation of cell death is blocked, while c-$FLIP_L$-mediated NFκB activation is encouraged (Chang et al., 2002; Peter and Krammer, 2003). The T-cell population is successfully proliferated as a result of two different interactions of caspase-8. On the other hand, T cells increasing in number die out if proliferation occurs, excessively. The primary role of caspase-8 is signal activation and proliferation. Only secondary events may turn these signals into death-induced mechanisms (Pop et al., 2011).

**4. Caspases in stem cell self-renewal and differentiation**

Maintaining tissue growth and homeostasis depends on the complex relationship between self-renewal, differentiation, and apoptosis of the stem cells. This strong relationship has led to the necessity of investigating the possible effect of caspases on regeneration. In 2008, Janzen et al. drew attention to the nonapoptotic effects of caspases by revealing that caspase-3 mediates differentiation of the hematopoietic stem cells.

Stem cells are known as cells that can self-renew, differentiate into specific cell types, and form clones (Can, 2014). The term 'self-renewal' can be defined as propagation via forming another self. This is a specific cellular process and leads to the persistence of both multipotency and the regenerative potential of the tissue. Two events occur in the process of self-renewal: first, cells enter the cell cycle and divide; and in the second step, one of the cells formed remains undifferentiated. Any problem that might occur in one of these two steps leads to a decrease in the number of stem cells and functional impairments may occur in the tissue. Within adult organisms, stem cells are located in specialized regions referred to as niches in every tissue. In normal homeostasis and during injury, these cells contribute to the repair of the damaged tissue by differentiating into the cell types of that tissue. The self-renewal ability of the stem cells is a result of extracellular signals derived from intracellular proteins and niche microenvironment (Fuchs and Chen, 2013).

In many tissues, the self-renewal of the stem cells is coordinated with tissue regeneration. Even though growth requirements and cellular hierarchy may alter based on tissue type, the frequency of self-renewal in adult stem cells solely depends on the need to differentiate (O'Brien et al., 2011). Based on the fact that differentiation of the stem cells is considered as a decrease in self-renewal capacity, the possibility that caspase-3 plays a critical role in stem cell functions was investigated. Fujita et al. (2008) showed that caspase activity takes place in the early stages of embryonic stem cell differentiation by using a caspase-3 specific cleavage sensor. They determined that embryonic stem cells that do not contain caspase-3 fail differentiation tests under in vitro conditions, and differentiation did not occur in vivo when they were transplanted. Investigators have suggested that caspase-3 exerts these effects by directly cleaving pluripotency factors and at this point Nanog is the primary substrate. They proved this hypothesis by investigating self-renewal in embryonic stem cells that contain caspase-3-resistant Nanog factor and showing that differentiation is suppressed. Likewise, studies conducted by Janzen et al. (2008) on caspase-3-null mice, have shown that lack of caspase-3 leads to an increase in the number of hematopoietic stem cells, while significantly decreasing the number of mature blood cells in circulation. On the other hand, there was no change in the number of apoptotic cells. When bone marrow isolated from caspase-3-null animals was transplanted into wild-type animals, abnormal hematopoietic lineage profiles were observed. All of these findings clearly suggest that caspase-3, which has a well-known apoptotic role, is also an essential protein in stem cell growth and differentiation.

Besides the Oct-4, Sox-2, and Nanog factor trio, known to play a role in regulating self-renewal, zinc finger DNA-binding protein Ronin prevents differentiation by suppressing genes such as transcription factors GATA-4 and -6, which induce differentiation. When differentiation begins, Ronin is broken down via caspase-3 (Can, 2014). This finding revealed that caspase-3 maintains a balance between self-renewal and differentiation via intracellular molecular interactions, and this model is called the "cell-autonomous" or "direct" model. Thus, caspase activity changes the behavior of the cell by modulating regulatory networks (Connolly et al., 2014) (Figure 2).

Especially in a number of studies done on model organisms, it has been shown that the activation of caspases plays a key role in tissue remodeling that occurs as a response to tissue damage by affecting cell proliferation and stem cell functions. For example, in *Drosophila*, mitotic figures are reassembled in response to cell death (Li et al., 2009). Moreover, apoptosis in *Planaria* is associated with tissue remodeling and regeneration (Pellettieri et al., 2010). Treatment with pan-caspase inhibitor leads to the prevention of regeneration of the head (Chera et al., 2009).

Studies done on snakes, flies, and rats have revealed that caspase-3 is a key molecule in regulating neurogenesis (D'Amelio et al., 2010). Fernando et al. (2005) suggested that caspase-3 does not only play a role in cell death, but also in neural stem cell differentiation. Using primary neural stem cells as an in vitro system, they determined that caspase-3 activity in neural progenitors is associated with neurogenesis. Inhibition of caspase-3 during neurosphere differentiation does not affect apoptosis; on the other hand, a decrease in the expression of proteins associated with differentiation and an arrest in differentiation have been reported. In an experimental stroke model, it was also indicated that, during remission, active caspase-3 levels in neural precursor cells increase and apoptosis is not involved in this increase. In the same study, it was determined that caspase-3 activity was inhibited and there was an increase in neural precursor cell proliferation and migration. In this mechanism, caspase-3 exerts its effect by suppressing Akt phosphorylation (Fan et al., 2014). It has been shown that besides caspase-3, caspase-9 also plays a role in the differentiation process of muscle progenitor cells into myotubes and myofibers (Fernando et al., 2002; Murray et al., 2008). Studies show that decreases in caspase-9 levels or the overexpression of Bcl-xL limit myoblast differentiation

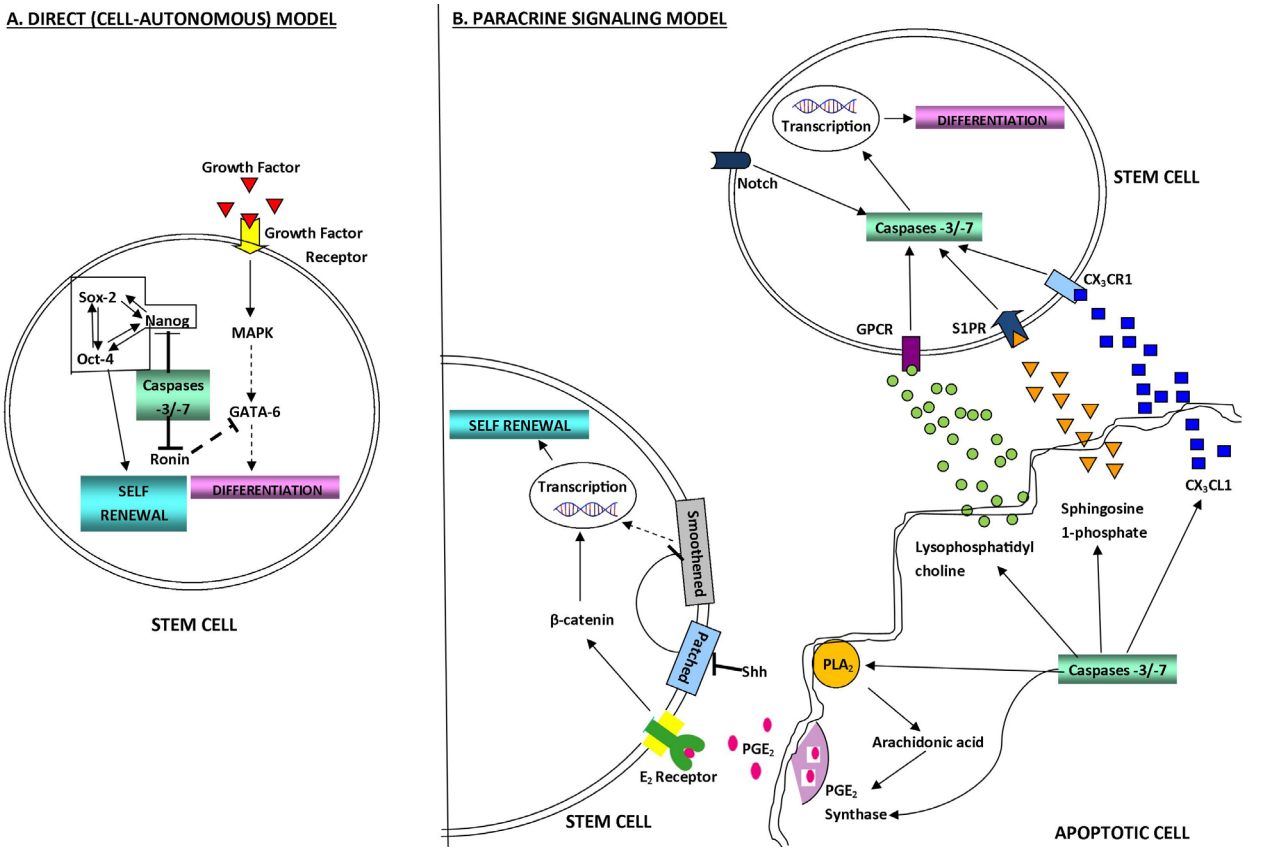


**Figure 2.** The proposed models related to stem cell self-renewal and differentiation. A) Direct (cell-autonomous) model: in addition to the Oct-4, Sox-2, and Nanog trio, whose roles are well known in regulation of stem cell self-renewal, Ronin is another important molecule that suppress differentiation by inhibiting transcription factors related to differentiation such as GATA-6. Ronin and Nanog cleaved by caspases. MAPK: Mitogen-activated protein kinase. B) Paracrine signaling model: active caspases cause synthesis and secretion of various signaling molecule such as $PGE_2$, lysophosphatidylcholine, sphingosine 1-phosphate, and $CX_3CL1$ in apoptotic cells. $PGE_2$ and Shh stimulate self-renewal in neighboring stem cells. On the other hand, lysophosphatidylcholine, sphingosine 1-phosphate, and $CX_3CL1$ initiate transcription of the gene related to differentiation through caspases in neighboring stem cells, and Notch has also been reported to show its effects in a similar way in this situation. Shh: Sonic Hedgehog, $PGE_2$: prostaglandin $E_2$, $CX_3CL1$: fractalkine, $CX_3CR1$: fractalkine receptor, GPCR: G protein-coupled receptor, S1PR: sphingosine 1-phosphate receptor. Adapted from Solá et al. (2012).

by decreasing the activity of caspase-3 (Murray et al., 2008). Caspase-3 activity also plays an important role in the osteogenic differentiation of mesenchymal stem cells, and in mice with impaired caspase-3, a decrease in bone marrow stem cell differentiation and a low bone mineral density were determined (Miura et al., 2004). Without any alteration in apoptotic cell death, caspase-2 and -8 also play a role in this process (Mogi and Togari, 2003). It was also shown that caspase-7 plays a role in odontoblast differentiation (Matalova et al., 2013).

In caspase-mediated regeneration, besides the direct effects of caspases within the cells, paracrine molecules released from apoptotic cells also play an important role. For example, lysophosphatidylcholine (Ryborg et al., 2004), sphingosine-1-phosphate (Mao and Obeid, 2008), and fractalkine ($CX_3CL1$; Koizumi et al., 2009) are produced by apoptotic cells and are well known as inflammatory molecules. It was also shown that they induce caspase-dependent differentiation (Figure 2).

The relationships between caspase-3 and the three predominant signaling pathways, namely Wnt/β-catenin, Notch, and Shh, are evaluated below.

Apoptotic cells activate the Wnt/β-catenin pathway in neighboring cells via Wnt3. Thus, apoptotic cells are determined as the origin of the signal leading neighboring nonapoptotic cells to regenerate. Investigators have administered *Hydra* with pan-caspase inhibitors and Wnt3 together and have proven that migration of β-catenin to the nucleus is stimulated and the activation of caspase-mediated Wnt/β-catenin pathway plays a key role in head regeneration (Chera et al., 2009). In another study, it was determined that caspase-3 leads to prostaglandin

$E_2$ ($PGE_2$) production and release from apoptotic cells, which caused the activation of the Wnt/β-catenin pathway in neighboring nonapoptotic cells (Castellone et al., 2005; Zhao et al., 2006; Goessling et al., 2009) (Figure 2). It has been shown that this mechanism also plays a role in wound healing in mammalian cells by increasing the proliferation of keratinocyte progenitor cells by caspase-3 and -7 (Li et al., 2010). It has also been shown that some molecules released by pancreatic beta cells during caspase-dependent apoptotic death induced proliferation and differentiation of the neighboring cells (Bonner et al., 2010). Findings of these studies clearly reveal that, in order to maintain tissue homeostasis and replace damaged cells with new ones, caspase-3- or -7-mediated paracrine signals play an important role in inducing proliferation, migration, and differentiation of stem cells and progenitor cells.

The Notch signaling pathway plays an important role in mammalian keratinocyte differentiation (Watt et al., 2008). A previous study revealed that the Notch signal is upregulated in embryonic keratinocytes and epidermis. In addition, the expression of caspase-3, which is described as the transcriptional target of Notch, increased, and this signal contributes a great deal to the terminal differentiation of embryonic keratinocytes. In the same study, it was shown that in the lack of in vivo caspase-3, proliferation increased and differentiation decreased (Okuyama et al., 2004). Similarly, Fischer et al. (2014) showed that, in zebrafish, the Tap63/p53>Notch>caspase-3 pathway is necessary for both the proliferation of keratinocytes located in the basal layer of tubercles and differentiation, which takes place in the upper layers following proliferation (Figure 2).

It has been shown that morphogen Shh stimulates cell division and prevents differentiation into multinucleated myotubes both in muscle satellite cells and C2C12 cells. In addition, it was determined in the same study that Shh restrains caspase-3 activation induced by serum deprivation. It has been stated that all of these changes were reversed by cyclopamine administration, which is an inhibitor of the Shh pathway. Based on this study, it may be suggested that Shh has proliferative and survival effects on satellite cells (Koleva et al., 2005).

**4.1. How can caspases regulate self-renewal and differentiation of stem cells?**

Within the scope of the studies mentioned above, this question comes to mind: Do caspases lead to stem cell differentiation by only suppressing self-renewal? These important events should be regulated by different aspects. The hypothesis that caspase-3 may interact with several factors to initiate the expression of genes that lead to differentiation of specific cell types has been suggested (Abdul-Ghani and Megeney, 2008). A finding that supports this hypothesis is that caspase-3-activated DNase activity leads to cell differentiation by increasing the expression of key regulatory genes (Larsen et al., 2010). Further important support of this hypothesis was put forward by Janzen et al. (2008), namely that a decrease in early B lymphocyte development, which is a very late step in the self-renewal process of hematopoietic stem cells, occurs with loss of caspase-3. In addition, caspase-8 deletion in bone marrow cells blocked the differentiation of monocytes into macrophages (Kang et al., 2004). These findings clearly reveal that caspases are key proteins that play a role in terminal differentiation besides suppressing self-renewal.

Without a doubt, among other questions that come to mind regarding this mechanism are "How does caspase-3 lead to a different cellular event in the stem cells?" and "How do differentiated cells limit the activity of caspase-3 without disrupting cellular integration?" The answers to these questions underlie the complex mechanistic interactions defining the fate of the stem cell. Markedly similar morphological and molecular events take place in apoptotic or differentiated cells. Among these, the most remarkable ones can be considered as the reassembly of the elements of the cytoskeleton and outstanding changes that occur in chromatin and nuclear structure with membrane fusion and fission (Fernando and Megeney, 2007). Caspase-3 contributes to the formation of these changes. So, is the efficacy of caspase-3 the same in both events? A few possible mechanisms related to the regulation of nonapoptotic caspase function involve temporary caspase activation, local caspase activation, and the regulation of endogen caspase inhibitors (Solá et al., 2013) (Figure 3). It is known that low and short-term caspase signals seen in differentiation programs cannot cleave enough death substrate. However, there is always a consistent amount of active caspase-3 present during apoptotic signaling (Ishizaki et al., 1998; Zermati et al., 2001). The mechanism related to the fact that caspase-3 mediates differentiation in stem cells instead of death can be provided by the findings obtained from studies done on model organisms. For example, in *Drosophila*, spermatid differentiation is entirely based on apoptotic signaling pathways (Huh et al., 2004). In this system, caspase activity is regulated by the degradation of ubiquitin-mediated caspase proteins (Arama et al., 2007) (Figure 3). Such a mechanism might be in action in order to retain the level of caspase activity only at a degree that finalizes spermatid differentiation. It is possible that there are number of similar control mechanisms found in the mammalian stem cells; however, there are not enough studies available on the subject yet. In a study that explained the temporary activation mechanism of caspases, it was reported that, on the contrary to apoptotic cell death signal, Bad is temporarily activated at a low level and Bax is not translocated into the mitochondria. As a result, intermediate levels of

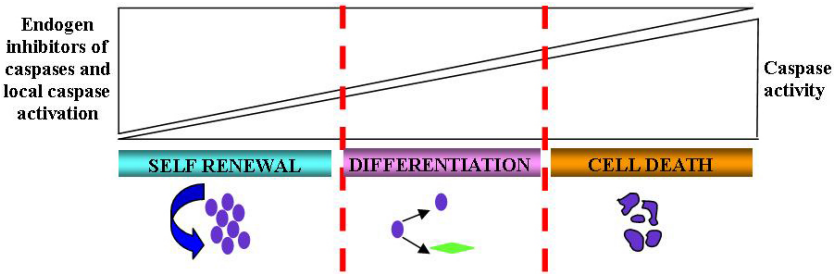


**Figure 3.** Possible mechanisms put forward regarding the regulation of caspase activity and the relevant cellular pathways without disturbing the cellular integrity. Specific cellular events depend on the subcellular localization and kinetics of caspase activity and the expression of endogenous caspase inhibitor levels.

activated caspase-3 lead to nonlethal cellular events (Jiao and Li, 2011). In some studies, it has been suggested that caspase-3 is always present in living cells; however, it is kept bound to its inhibitors and is temporarily released for essential nonapoptotic functions such as caspase-mediated neural differentiation (Huesmann and Clayton, 2006). Based on another approach, access to caspase substrate regulates the cellular event, which will be terminated by the caspases. For example, it has been shown that, during the denucleation of erythroids, chaperone protein Hsp70 protects GATA-1, the regulatory transcription factor of erythroid maturation, from proteolysis (Ribeil et al., 2007). It has been suggested that specific subcellular localization of caspases plays an important role in determining which cellular events caspases will mediate, and their localization is closely related to IAP (Plenchette et al., 2004). During spermatogenesis, regulation of the nonapoptotic function of caspases is done via the ubiquitin proteasome system, which targets IAP-like proteins; hereby, caspases can leave their inhibitory proteins and remain free (Arama et al., 2007; Kaplan et al., 2010). In conclusion, all of these findings show that, during cell remodeling, caspase activity is regulated by a number of mechanisms synergistically. Caspases cleave but do not always degrade their substrate, and sometimes they regulate the functions and localization of proteins in this way.

## 5. Caspases in tissue repair

Repair is generated in tissue healing after any insult that causes tissue destruction when the damage cannot be ameliorated via cell/tissue renewal and regeneration. A balance between repair and regeneration is based on the regeneration ability of the tissue and the extent of the injury (Kayalar and Oztay, 2014). In the healing process, repair restores normal structures and functions in tissues/organs that do not have proliferation and regeneration abilities or that have lost these abilities due to pathological stimulus. Repair is characterized by an excessive accumulation of extracellular matrix (ECM) components and scar formation, and then resolution of scar tissue begins. Thus, the damaged tissue is restored at the end of repair (Duffield et al., 2013). Typical tissue healing/repair is generally divided into three phases: 1) inflammation process, 2) scar formation, and 3) tissue remodeling, although there is no definite separation among the phases. It is thought that one phase acts as a stimulant or initiator for the following phase. Many matrix proteins, growth factors, cytokines, chemokines, and proteases are effective through all phases of the repair process (Eming et al., 2014). Nowadays, caspases from proteases are coming into prominence with unexpected biological effects in addition to their apoptotic roles (Connolly et al., 2014). Cumulative data suggest that caspases may be essential proteases in the regulation and modulation of the repair process. These data are provided and discussed below in more detail.

Death of epithelial, endothelial, and mesenchymal cells occurs via distinct modes of cell death, such as necrosis and apoptosis during irreversible tissue injury caused by ischemia, trauma, thermal injury, infectious agents, and other similar insults. Apoptotic cell death, which was induced by intrinsic or extrinsic signals (FasL-mediated apoptosis), was determined in lung, liver, kidney, and pancreas injuries (Gezginci-Oktayoglu et al., 2008, 2011; Oztay et al., 2010; Gezginci-Oktayoglu and Bolkent, 2012). Caspase-8 may either directly induce apoptosis by the activation of effector caspases or indirectly stimulate the mitochondrial pathway of cytochrome *c* release and caspase-9 activation (Shalini et al., 2015). Poly ADP ribose polymerase is a well-known enzyme for DNA repair process and is inactivated by caspase-3 cleavage during apoptotic death (Luo and Kraus, 2012). In the damaged tissue following injury, a protective response develops to eliminate the initial cause of cell injury, to remove debris of cells and tissues, and to initiate the process of repair. This first phase of repair is called the inflammation process. Indeed, it is well known that apoptosis does not result in an inflammatory response, because dead cells are rapidly cleared by phagocytic cells. So, how are caspases able to initiate an immune response? Vascular response to injury allows platelet aggregation, clot formation, and subsequently

development of a provisional ECM. Platelets, basophiles, and resident cells localized in the tissue secrete various cytokines, chemoattractants, inflammatory mediators, platelet-derived growth factor, TGF-β, and proteases. Thus, phagocytic and inflammatory cells, including neutrophils, monocytes, lymphocytes, eosinophils, and basophils, filtrate easily into the site of injury. Monocytes become macrophages. The differentiation of macrophage colony-stimulating factor-treated monocytes into macrophages is realized by the activation of caspase-3 and -9 in the absence of apoptosis (Sordet et al., 2002). Additionally, the inflammatory caspase, caspase-11, leads to macrophage migration by regulating actin dynamics in inflammation (Li et al., 2007). Activated macrophages and neutrophils digest dead and dying cells, fibrin mesh, and clot residues. Recent reports have shown that apoptotic cells may also send "find me" signals. In the response of these signals, phagocytic cells migrate toward dying cells (Gregory and Pound, 2011). Furthermore, Cullen et al. (2013) determined the secretion of inflammatory cytokines and chemoattractants including IL-6, IL-8, the chemokine ligand-1, monocyte chemoattractant protein-1, and granulocyte-macrophage colony-stimulating factor, which attracted granulocytes, T cells, monocytes, and macrophages through FasL-induced apoptotic cells. Based on these data, it is suggested that tissue repair is directed by these molecules via the infiltration and activation of phagocytic and inflammatory cells, and the initiation of the immune system. The other type of caspase that is effective in inflammatory response is caspase-1. Caspase-1 activation is necessary for the production of inflammatory cytokines such as IL-1β and IL-18 in macrophages during innate immune response. IL-1β is a lymphocyte mitogen, while IL-18 induces the release of interferon-gamma that plays an important role in activating the macrophages or other cells. In the absence of caspase-11, which is critical for caspase-1 activation, defects in IL-1β production were detected (Kayagaki et al., 2011). These data mentioned above clearly show that caspases can directly or indirectly regulate the inflammation processes of repair (Table).

The complex interaction of the chemical mediators in the inflammatory phase stimulates the proliferative response of the damaged tissue. Fibroblasts migrate into the provisional matrix, and subsequently they proliferate and produce de novo ECM. The proliferation of fibroblasts and their differentiation into myofibroblasts are induced by TGF-β, platelet-derived growth factor, connective tissue growth factor, and fibroblast growth factor secreted from activated epithelial cells, platelets, wound macrophages, and the other parenchymal cells (Antoniou et al., 2007; Oztay and Yilmaz, 2015). Caspase-3 and -7 activation in apoptotic cells promotes the proliferation of surrounding cells during wound healing (Li et al., 2010). However, there is no direct evidence of caspase-induced fibroblast proliferation in tissue repair. On the other hand, several studies have noted the role of caspase in cell motility and migration. Procaspase-3 has a nonapoptotic function; it regulates the secretion of fibronectin and influences morphology, adhesion, and migration of mouse embryonic fibroblasts (Brentnall et al., 2014). After fibroblast proliferation, fibroblasts simultaneously acquire a myofibroblastic phenotype. IL-1β and/or IL-

**Table.** Caspases can directly or indirectly regulate and modulate the tissue repair.

| Tissue response to injury | Phases of healing | Caspase-dependent possible cellular events | Relevant caspases | References |
|---|---|---|---|---|
| Repair | Inflammation | Apoptotic cell death<br>Immune cell infiltration<br>Immune cell activation<br>Macrophage differentiation | Caspase-3 and -8<br>Caspase-3, -9, and-11<br>Caspase-1 and -11<br>Caspase-3 and -9 | Oztay et al. (2010)<br>Uhal et al. (1998)<br>Li et al. (2007)<br>Cullen et al. (2013)<br>Kayagaki et al. (2011)<br>Sordet et al. (2002) |
| | Scar formation | Fibroblast migration<br>Myofibroblast differentiation | Caspase-3<br>Caspase-1 | Brentnall et al. (2014)<br>Artlett et al. (2011) |
| | Tissue remodeling | Resolution of inflammation by apoptosis<br>Apoptosis of fibroblast/myofibroblast | Caspase-8<br>Caspase-3 | Conus et al. (2008)<br>Liu et al. (2014) |
| Fibrosis | Persisted tissue damage<br>Chronic inflammation<br>Induced cell proliferation<br>Excessive accumulation of ECM components | Induced apoptosis of epithelial cells<br>Apoptosis resistance of myofibroblast | FasL-mediated apoptosis<br>Caspase-8-cFLIP balance | Uhal et al. (1998)<br>Santiago et al. (2004) |

18 can mediate collagen expression via the induction of TGF-β. The inhibition of caspase-1 resulted in inhibition of collagen, IL-1β, and IL-18 secretion in dermal and lung fibroblasts of patients with systemic sclerosis. In addition, dermal fibroblasts obtained from patients with systemic sclerosis, treated with a caspase-1 inhibitor, exhibited decreased myofibroblast differentiation (Artlett et al., 2011). Upon vessel regression, pericytes may be released and develop myofibroblast features via paracrine signals from apoptotic endothelial cells, further encouraging the development of scar formation (Stoneman et al., 2009). Fibroblasts, and particularly myofibroblasts, which are resistant to apoptosis by downregulating caspase-3, produce and secrete a lot of collagen (Marcotte et al., 2004) (Table). Thus, the damaged tissue will be repaired with a scar, which is not a 'like for like' replacement of the original tissue.

During the resolution of the scar tissue, the disappearance of immune cells from the site of injury, the deactivation of macrophages, the reduction of hyperproliferation through apoptosis, and the digestion of excessive ECM components accumulated in the interstitium are induced in order to allow tissue remodeling. Neutrophils are cleared from the wound site at least in part by apoptosis. It has been noted that cathepsin D, by initiating neutrophil apoptosis during the resolution of inflammation, induces caspase-8 activation (Conus et al., 2008). Polymorphonuclear apoptotic cells are removed by macrophages (Herold et al., 2011). It was detected that the remaining neutrophils and macrophages returned to the circulatory system (Schwab et al., 2007). Additionally, macrophages are deactivated by antiinflammatory cytokines, glucocorticosteroids, cell–cell contact, or phagocytosis (Ma et al., 2003). Apoptosis is also activated in order to rapidly remove the fibroblasts/myofibroblasts increasing in number (Table). The removal of the excess myofibroblasts via apoptosis is accepted as a normal mechanism in skin wound healing models (Jun and Lau, 2010). Darby et al. (2002) detected that reduced growth factor expression, increased extracellular matrix turnover, and induced nitrosative stress could stimulate apoptosis in myofibroblasts. The inhibition of myofibroblast differentiation is also important in tissue remodeling. Liu et al. (2014) found that the deficiency of the smad3-dependent TGF-β signal pathway, which suppressed myofibroblast differentiation, promoted myofibroblast apoptosis by activating the caspase-3 pathway. It seems that caspase maintains the homeostasis of the wound environment by balancing cell elimination with cell proliferation. Finally, the resolution of scar tissue is completed by the matrix metalloproteinase-mediated degradation of excessive ECM components.

Prolonged exposure to potentially injurious agents and chronic/nonresolving inflammation can result in fibrosis. Fibrosis is characterized by an increase in the number of fibroblasts and the accumulation of ECM components such as interstitial collagens, fibronectin, proteoglycans, and hyaluronic acid in the ECM in wound healing and liver and lung fibrosis. Fibrosis can mostly occur in the liver, kidneys, lungs, and skin (Bataller and Brenner, 2005; Gezginci and Bolkent, 2007; Hewitson, 2012; Ovet and Oztay, 2014; Bagnato et al., 2015). Fibrosis may refer to a pathophysiological mechanism underlying organ failure. An important result indicates an interaction between altered apoptosis and fibrosis in nearly all types of fibrosis. Alveolar epithelial apoptosis adjacent to underlying myofibroblasts was detected in the lung tissue removed from patients with idiopathic pulmonary fibrosis (IPF) (Uhal et al., 1998). Additionally, it was found that the fibroblasts isolated from lung biopsy and human lung myofibroblasts could produce factors, such as angiotensin peptides, capable of killing alveolar epithelial cells by apoptosis in pulmonary fibrosis (Uhal et al., 1995; Wang et al., 1999). Hagimoto et al. (1997) detected that FasL-mediated apoptosis induced the damage of alveolar epithelial cells, and ligation of the Fas antigen resulted in pulmonary fibrosis in mice, as well. Treatment with the broad spectrum caspase inhibitor Z-Val-Ala-Asp-fluoromethyl ketone inhibited bleomycin-induced apoptosis of alveolar epithelial cells by preventing subsequent collagen accumulation in rat lung with fibrosis (Adamson and Bowden, 1974). Based on results of the studies cited above, it can be suggested that caspase-3, -8, and -9 probably modulate FasL-induced apoptosis of alveolar epithelial cells in pulmonary fibrosis (Table). It is known that the lungs of IPF patients present an increase in epithelial apoptosis together with resistance to apoptosis in myofibroblasts. IL-6 inhibits apoptosis by inducing expression of Bcl-2, which is an antiapoptotic protein, in primary fibroblasts of patients with IPF (Moodley et al., 2003). Subsequently, it was reported that TGF-β, thrombin, and insulin-like growth factor-1 mediate resistance to apoptosis in lung fibroblast by the activation of prosurvival phosphatidylinositol 3′-kinase (PI3K)-Akt signaling pathway (Kulasekaran et al., 2009). Additionally, resistance to FasL-mediated apoptosis in fibroblasts of patients with IPF developed with increased expression of X-linked inhibitors of apoptosis and $cFLIP_L$ (Tanaka et al., 2002). Santiago et al. (2004) demonstrated that $cFLIP_L$ downregulation sensitized human dermal fibroblasts to FasL-induced apoptosis. They also detected that the $cFLIP_L$ and caspase-8 balance regulated resistance to apoptosis in fibroblasts by TGF-β and IL-10, which upregulated their susceptibility to FasL-induced cell death. On the other hand, several studies have clearly indicated that substances secreted from dying apoptotic cells are affected by adjacent

cells via paracrine signaling. For example, $PGE_2$, as its production pathway is directly controlled by caspase-3 (Boland et al., 2013), secreted from apoptotic cells can stimulate the Wnt/β-catenin signal pathway in adjacent cells. In the past decade, the role of the Wnt/β-catenin signal pathway in tissue fibrosis has been investigated in great detail. This pathway is an important stimulator of epithelial-mesenchymal transition. The Wnt/β-catenin signal-dependent epithelial-mesenchymal transition contributes to tissue fibrosis (Konigshoff et al., 2009). It is still unknown whether apoptotic cells can induce Wnt/β-catenin signal-mediated fibrosis or not.

**6. Caspases in tumor cell repopulation and motility**

Although caspase activation is a desired phenomenon due to induction of cell death, and particularly apoptosis, recent findings indicate that nonapoptotic levels of certain caspases could be related to tumor repopulation after radiotherapy or chemotherapy. Besides, increased expression of caspases has been shown in various types of tumor tissues, such as breast cancer tissue (Yang et al., 2003), and these nonapoptotic high levels of caspases have been associated with poor prognosis and remain to be further investigated.

Due to the fact that tumor relapse after radiotherapy is a serious problem that must be overcome, molecular mechanisms of induced cell proliferation by dying cells have been studied in recent years in in vitro and xenograft models. Similar pathways in tissue regeneration and repair, as mentioned earlier, were also found in the repopulation of tumors after being exposed to radiation. It was observed that viable cells have active caspase-3 but not caspase-8. In these cells, caspase-3 regulates growth by stimulating $PGE_2$ expression through activating calcium-independent phospholipase $A_2$ ($iPLA_2$). Absence or inhibition of caspase-3 using shRNA or caspase $3^{-/-}$ mouse models abolished the release of $PGE_2$ induced by ionizing radiation and mitogenic potential of irradiated cells (Huang et al., 2011). Another study also uncovered the role of caspase-3 in melanoma cell regrowth after treatment with anticancer agents, vemurafenib and indomethacin, or radiation in a similar pathway (Donato et al., 2014). In addition, caspase-3 is not only activated in dying tumor cells, but also in other cells in the tumor microenvironment, such as endothelial cells (Mao et al., 2013) and fibroblasts (Huang et al., 2011), in order to stimulate tumors cells for repopulation in a similar signaling pathway. It has been observed that molecules in charge of stimulating living tumor cells vary depending on different types of cancer cells. Cheng et al. (2015) observed that dying pancreatic cancer cells have active caspase-3, caspase-7, and protein kinase Cδ, and these active molecules lead to phosphorylation of Akt and p38 mitogen-activated protein kinase (MAPK), involved in cell proliferation. It was found that most of the tumor tissues have a subpopulation of tumor cells called cancer stem cells and these stem cells have self-renewal capacity, are resistant to radiotherapy and chemotherapy, proliferate and drive continued expansion of malignant cells, and serve as a reservoir of cells that cause tumor recurrence after therapy (Ailles and Weissman, 2007). Caspase-mediated paracrine signaling may also stimulate cancer stem cells and lead to tumor repopulation. Uncovering these molecular pathways contributes to therapy, especially in patients with high caspase activity in their tumor tissues.

Besides inducing roles for cell growth, it has been detected that low levels of caspases are also involved in cell motility. The basal levels of caspase-3 and -8 in glioma cells have been shown to be associated with cell motility, and motility-associated gelsolin cleaved by these caspases may promote migration and invasion (Gydnia et al., 2007). The chemical inhibitor of caspases or gene ablation by siRNA attenuated cell invasion and migration. Liu et al. (2013) also found that the responsible caspase for cell motility is caspase-3 by activating matrix metalloproteinase-2. Caspase-3 also plays a role in ovarian carcinoma cell migration by activating $iPLA_2$ and active $iPLA_2$ generates arachidonic acid and lysophosphatidic acid, which are involved in cell migration towards laminin and blocking apoptosis by Akt, respectively (Zhao et al., 2006). Consistent with these findings, nonapoptotic caspase expression causes cell invasion through the JNK pathway, increasing the expression of matrix metalloproteinase-1 in the *Drosophila* model of invasion (Rudrapatna et al., 2013). It has also been observed that caspase-8 promotes cell migration through localizing peripherally to constitute a complex with focal adhesion kinase and calpain-2, and the catalytic domain is not necessary for this nonapoptotic function (Senft et al., 2007; Barbero et al., 2009). In addition to the role in migration, another mission of caspase-8 has been unveiled. Exposing of sublethal doses of TRAIL, which is used to overcome resistance in intrinsic apoptotic pathways, caused DNA breaks in glioma and mouse embryonic fibroblasts (Lovric and Hawkins, 2010). It has been observed that these mutations occur through the activation of caspase-activated DNase (CAD), which is inhibited by active caspase-8 substrate, the inhibitor of CAD. Thus, surviving doses of TRAIL provokes mutagenesis through caspase-8 activation. In a more recent study, Liu et al. (2015) showed that sublethal activation of caspase-3, after exposure to ionizing radiation, leads to genomic instability, oncogenic transformation, and increased tumorigenic nature in MCF10A mammalian cells, and the downstream effector of caspase-3 is EndoG in this damage. Absence of caspase-3 reduced these alterations. Similarly, radiation therapy-induced caspase-3 may also amplify tumorigenic properties of surviving

cancer cells by mutagenesis and further investigation is required.

These unusual functions of caspases that have emerged in recent years raise the following question: How do cancer cells sustain low levels of caspases and avoid cell death? Cancer cells are able to benefit from multifunctional roles of caspases by expressing high levels of antiapoptotic molecules. Yang et al. (2003) showed that surviving and X-linked IAP, two members of the inhibitors of apoptosis protein family, were expressed in high levels, and downregulation of these molecules induced apoptotic cell death in tumor cells. Overall, targeting caspases during cancer therapy must be a novel approach. It has been observed that administration of a pan-caspase inhibitor, Z-VAD, increased the radiosensitivity of breast and lung cancer in both in vivo and xenografts models (Kim et al., 2008; Moretti et al., 2009), and a similar approach could be considered for patients. For an effective complementary therapy, the use of inhibitors that specifically target molecules activated by caspases such as cyclooxygenases, $PGE_2$ receptor, protein kinase C, phospho-Akt, or p38 MAPK could also be taken into consideration during radiotherapy or chemotherapy. Sensitivity to therapies could thus be increased by reducing cell motility, mutagenesis, and compensatory proliferation evolutionarily conserved.

**7. Caspases in stem cell aging**

It is common knowledge that biological aging of stem cells causes ineffective regenerative responses to tissue injury, resulting in organ failure in elderly people. On the other hand, the success of stem cell therapy is closely related to cell properties, which can vary based on the age of donors. The molecular mechanism of the aging process in stem cells is poorly understood, which limits cell-based therapies. The factors contributing to stem cell aging are increasing aggregation of damaged proteins, mitochondrial dysfunction, reactive oxygen species, epigenetic alterations, DNA damage, and extracellular signals, and these factors affect stem cell activity (Oh et al., 2014).

It was observed that there are age-related gene expression changes in mesenchymal stem cells. The expression of the *p53/p21* gene and genes related to apoptosis, such as *Fas*, *Bax*, *Bad*, *Apaf-1*, and *caspase-8*, were decreased in bone marrow mesenchymal stem cells of aged individuals (Wilson et al., 2010). On the other hand, Alt et al. (2012) also found that aging caused decrease in the expression of *p53* and *caspase-3*, *-8*, and *-9* genes and increase in *Bcl2* and *Bax* gene expression. These data suggest that aging results in replicative senescence due to loss of p53 and resistance to apoptosis, and it may also provide oncogenic characters to stem cells, probably for transforming to cancer stem cells. Due to acquired tolerance to molecular damage such as DNA damage and defective proteins, stem cells with the senescence phenotype have less proliferative capacity and the regeneration in tissues decreases with aging. On the other hand, studies with satellite cells obtained from rats of different ages have shown that more caspase activity is found related to aging. These findings suggest that these progenitor cells tend towards apoptotic cell death, which leads to muscle loss (Jejurikar et al., 2006). A recent study has also shown that the expression of cell death genes and caspase-2, -3, -6, -7, -9, and caspase-3 activity increased in satellite cells obtained from aged donors, and aged satellite cells are more prone to apoptosis, as demonstrated by flow cytometer analysis of annexin V/propidium iodide staining and terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling technique (Fulle et al., 2013). The endothelial progenitor cells are involved in vascular repair and, by aging, these cells have more susceptibility to apoptosis induced by staurosporine due to increased activity of caspase-3 and attenuated expression of antiapoptotic proteins related to the PI3K/Akt signaling pathway (Kushner et al., 2011). According to these findings, the roles of caspases related to cell death in aging may be different in stem cells and progenitor cells, leading to loss of regeneration potency in tissues.

**8. Future directions**

Caspase-mediated cell death and inflammation can be accepted as one of basic causes of diseases like myocardial infarction, stroke, sepsis, and Alzheimer and Parkinson diseases. Hence, the attenuation and blocking of caspases' activities via caspase inhibitors has been tested as a main therapeutic approach for therapy of these diseases for the past 20 years. The induction of apoptotic cell death is a promising therapeutic approach in cancer, which is characterized by uncontrolled cell proliferation. Moreover, apoptotic cell death has occurred during the reduction of inflammation and the resolution of scar tissue, as well. Although direct use of caspase inhibitors is preferred, especially to regulate the caspase efficacy in the pharmacologic modulation of cell death, this blockage can also trigger caspase-independent cell deaths, so it is not considered as a very accurate approach. For this purpose, while discovering drugs that inhibit inflammatory caspases selectively in the therapy of diseases like rheumatoid arthritis, and in the therapy of cancer and viral infections, selective activation of caspases can be a more effective approach. Effective therapeutic approaches such as antibody application, which is specific to active caspases, and targeting cancer cells selectively in chemotherapy should be taken into consideration for cell therapies.

Recent studies have shown that apoptotic cells are not silent; on the contrary, they regulate the proliferation, differentiation, and migration of neighboring cells in a paracrine manner, by the secretion of various substances. Caspases are important for the formation of new cells instead of damaged cells in apoptosis-induced compensatory proliferation. Proliferative caspases can be effective in therapeutic approaches to several diseases via understanding of their molecular mechanisms. The regeneration capacity in tumor tissue after radiotherapy and chemotherapy has been detected and dying cells emit proliferative signals that attenuate the effectiveness of the therapy. Inhibition of caspases or downstream molecules activated by caspases may attenuate tumor regrowth, and the use of inhibitors as adjuvants may also decrease tumor cell motility and mutagenesis. Additionally, stem cells have been considered as target cells for therapy of various diseases. Unfortunately, stem cell therapy is not satisfactory, safe, or convenient for clinical applications yet. The major problem is to maintain a very small amount of healthy and functional stem cells after transplantation; in other words, differentiation cannot be obtained. The emergence of new roles of caspases, such as suppressing stem cell self-renewal and inducing differentiation, have led to changes in the perspective on these proteins. In this context, new cells directed to specific terminal differentiation can be produced by the discovery and implementation of IAP-like proteins, which can keep caspases at a certain location and low level of transient activation. These newly differentiated cells produced under in vitro conditions can be transplanted to patients. Alternatively, patients can be treated with such new agents to induce differentiation endogenously. After all, the discovery and implementation of cell-targeted temporary activators of caspases hold promise for stem cell-based cell therapy.

Response to tissue injury is directed toward either regeneration or repair of the tissue. Repair is a complex processes, which is mediated by epithelial, mesenchymal, and inflammatory cells and guided by several growth factors, cytokines, chemokines, and soluble proteins, and the proliferation, death, migration, and differentiation of cell and ECM remodeling occur. A growing body of evidence suggests that caspases can regulate and modulate every phase of repair by inducing the secretion of inflammatory cytokines and chemokines from apoptotic or inflammatory cells, cell migration, and immune cell infiltration. Although caspases have been considered as cell killers in various phases of repair in general, the effect of caspases playing a nonapoptotic role is still unclear on the scar resolution, tissue remodeling, and fibrosis of injured tissue in repair. For this reason, future research is need for illumination of this situation.

In conclusion, caspase-mediated cell death and the nonapoptotic response of cells are very important in tissue regeneration and repair. For this reason, caspase-targeted therapeutic approaches should come into prominence for the regression of tissue damage and disease progression. Although the therapeutic use of caspase inhibitors provides hopeful results in the short term in experimental studies, this treatment may lead to unwanted side effects due to ignoring the nonapoptotic roles of caspases. At this point, the level of caspases plays a crucial role in the direction of cells towards either death or regenerative and restorative signaling. If caspases' temporary activation, localization, and relationships with inhibitors are known in detail and they are successfully manipulated, then effective use of caspase-targeted therapy may be possible in the future.

## References


Aachoui Y, Sagulenko V, Miao EV, Stacey KJ (2013). Inflammasome mediated pyroptotic and apoptotic cell death and defense against infection. Curr Opin Microbiol 16: 319–329.

Abdul-Ghani M, Megeney LA (2008). Rehabilitation of a contract killer: caspase-3 directs stem cell differentiation. Cell Stem Cell 2: 515–516.

Adamson YR, Bowden DH (1974). The type 2 cell as progenitor of alveolar epithelial regeneration. A cytodynamic study in mice after exposition to oxygen. Lab Invest 30: 35–42.

Ailles LE, Weissman IL (2007). Cancer stem cells in solid tumors. Curr Opin Biotechnol 18: 460–466.

Alt EU, Senst C, Murthy SN, Slakey DP, Dupin CL, Chaffin AE, Kadowitz PJ, Izadpanah R (2012). Aging alters tissue resident mesenchymal stem cell properties. Stem Cell Res 8: 215–225.

Antoniou KM, Pataka A, Bouros D, Siafakas NM. Pathogenetic pathways and novel pharmacotherapeutic targets in idiopathic pulmonary fibrosis (2007). Pulm Pharmacol Ther 20: 453–461.

Arama E, Bader M, Rieckhof GE, Steller H (2007). A ubiquitin ligase complex regulates caspase activation during sperm differentiation in *Drosophila*. PLoS Biol 5: e251.

Artlett CM, Sassi-Gaha S, Rieger JL, Boesteanu AC, Feghali-Bostwick CA, Katsikis PD (2011). The inflammasome activating caspase 1 mediates fibrosis and myofibroblast differentiation in systemic sclerosis. Arthritis Rheum 63: 3563–3574.

Bagnato GL, Roberts WN, Fiorenza A, Arcuri C, Certo R, Trimarchi F, Ruggeri RM, Bagnato GF (2015). Skin fibrosis correlates with circulating thyrotropin levels in systemic sclerosis: translational association with Hashimoto's thyroiditis (in press).

Barbero S, Mielgo A, Torres V, Teitz T, Shields DJ, Mikolon D, Bogyo M, Barilà D, Lahti JM, Schlaepfer D et al. (2009). Caspase-8 association with the focal adhesion complex promotes tumor cell migration and metastasis. Cancer Res 69: 3755–3763.

Bataller R, Brenner DA (2005). Liver fibrosis. J Clin Invest 115: 209–218.

Beisner DR, Ch'en IL, Kolla RV, Hoffmann A, Hedrick SM (2005). Cutting edge: innate immunity conferred by B cells is regulated by caspase-8. J Immunol 175: 3469–3473.

Berghe V, Linkermann T Jouan-Lanhauet A, Walczak S, Vandenabeele P (2014). Regulated necrosis the expanding network of non-apoptotic cell death pathways. Nat Rev Mol Cell Biol 15: 135–147.

Bergmann, A, Steller H (2010). Apoptosis, stem cells, and tissue regeneration. Sci Signal 3: 8.

Bergsbaken T, Fink SL, Cookson BT (2009). Pyroptosis: host cell death and inflammation. Nat Rev Microbiol 7: 99–109.

Boatright KM, Deis C, Denault JB, Sutherlin DP, Salvesen GS (2004). Activation of caspases-8 and -10 by FLIP(L). Biochem J 382: 651–657.

Boland K, Flanagon L, Prehnt JHM (2013). Paracrine control of tissue regeneration and cell proliferation by caspase-3. Cell Death Dis 4: e725.

Bonner C, Bacon S, Concannon CG, Rizvi SR, Baquié M, Farrelly AM, Kilbride SM, Dussmann H, Ward MW, Boulanger CM et al. (2010). INS-1 cells undergoing caspase-dependent apoptosis enhance the regenerative capacity of neighboring cells. Diabetes 59: 2799–2808.

Bosch M, Serras F, Martín-Blanco E, Baguñà J (2005). JNK signaling pathway required for wound healing in regenerating *Drosophila* wing imaginal discs. Dev Biol 280: 73–86.

Brentnall M, Weir DB, Rongvaux A, Marcus AI, Boise LH (2014). Procaspase-3 regulates fibronectin secretion and influences adhesion, migration and survival independently of catalytic function. J Cell Sci 127: 2217–2226.

Can A (2014). Kök Hücre. Biyolojisi, Türleri ve Tedavide Kullanımları. 1st ed. Ankara, Turkey: Akademisyen Tıp Kitapevi (in Turkish).

Castellone MD, Teramoto H, Williams BO, Druey KM, Gutkind JS (2005). Prostaglandin E2 promotes colon cancer cell growth through a Gs-axin-beta-catenin signaling axis. Science 310: 1504–1510.

Chang DW, Xing Z, Pan Y, Algeciras-Schimnich A, Barnhart BC, Yaish-Ohad S, Peter ME, Yang X (2002). c- FLIP(L) is a dual function regulator for caspase-8 activation and CD95-mediated apoptosis. EMBO J 21: 3704–3714.

Cheng J, Tian L, Ma J, Gong Y, Zhang Z, Chen Z, Xu B, Xiong H, Li C, Huang Q (2015). Dying tumor cells stimulate proliferation of living tumor cells via caspase-dependent protein kinase Cδ activation in pancreatic ductal adenocarcinoma. Mol Oncol 9: 105–114.

Chera S, Ghila L, Dobretz K, Wenger Y, Bauer C, Buzgariu W, Martinou JC, Galliot B (2009). Apoptotic cells provide an unexpected source of Wnt3 signaling to drive *Hydra* head regeneration. Dev Cell 17: 279–289.

Chun HJ, Zheng L, Ahmad M, Wang J, Speirs CK, Siegel RM, Dale JK, Puck J, Davis J, Hall CG et al (2002). Pleiotropic defects in lymphocyte activation caused by caspase-8 mutations lead to human immunodeficiency. Nature 419: 395–399.

Connolly PF, Jäger R, Farnhead HO (2014). New roles for old enzymes: killer caspases as the engine of cell behavior changes. Front Physiol 5: 1–8.

Conus S, Perozzo R, Reinheckel T, Peters C, Scapozza L, Yousefi S, Simon HU (2008). Caspase-8 is activated by cathepsin D initiating neutrophil apoptosis during the resolution of inflammation. J Exp Med 205: 685–698.

Cullen SP, Henry CM, Kearney CJ, Logue SE, Feoktistova M, Tynan GA, Lavelle EC, Leverkus M, Martin SJ (2013). Fas/CD95-induced chemokines can serve as "find-me" signals for apoptotic cells. Mol Cell 49: 1034–1048.

D'Amelio M, Cavallucci V, Cecconi F (2010). Neuronal caspase-3 signaling: not only cell death. Cell Death Differ 17: 1104–1114.

Darby IA, Bisucci T, Pittet B, Garbin S, Gabbiani G, Desmouliere A (2002). Skin flap-induced regression of granulation tissue correlates with reduced growth factor and increased metalloproteinase expression. J Pathol 197: 117–127.

Delavallée L, Cabon L, Galán-Malo P, Lorenzo HK, Susin SA (2011). AIF-mediated caspase-independent necroptosis: a new chance for targeted therapeutics. Life 63: 221–232.

Denes A, Lopez-Castejon G, Brough D (2012). Caspase-1: is IL-1 just the tip of the ICEberg? Cell Death Dis 3: e338.

Dohrman A, Kataoka T, Cuenin S, Russell JQ, Tschopp J, Budd RC (2005). Cellular FLIP (long form) regulates CD8+ T cell activation through caspase-8-dependent NF-kappa B activation. J Immunol 174: 5270–5278.

Donato AL, Huang Q, Liu X, Li F, Zimmerman MA, Li CY (2014). Caspase 3 promotes surviving melanoma tumor cell growth after cytotoxic therapy. J Invest Dermatol 134: 1686–1692.

Duffield JS, Lupher M, Thannickal VJ, Wynn TA (2013). Host responses in issue repair and fibrosis. Annu Rev Pathol 8: 241–276.

Ellis HM, Horvitz HR (1986). Genetic control of programmed cell death in the nematode *C. elegans*. Cell. 44: 817–829.

Eming SA, Martin P, Tomic-Canic M (2014). Wound repair and regeneration: mechanisms, signaling, and translation. Sci Transl Med 6: 265sr6.

Fan W, Dai Y, Xu H, Zhu X, Cai P, Wang L, Sun C, Hu C, Zheng P, Zhao BQ (2014). Caspase-3 modulates regenerative response after stroke. Stem Cells 32: 473–486.

Fan Y, Bergmann A (2008a). Apoptosis-induced compensatory proliferation. The Cell is dead. Long live the Cell! Trends Cell Biol 18: 467–473.

Fan Y, Bergmann A (2008b). Distinct mechanisms of apoptosis-induced compensatory proliferation in proliferating and differentiating tissues in the *Drosophila* eye. Dev Cell 14: 399–410.

Fernando P, Brunette S, Megeney LA (2005). Neural stem cell differentiation is dependent upon endogenous caspase 3 activity. FASEB J 19: 1671–1673.

Fernando P, Kelly JF, Balazsi K, Slack RS, Megeney LA (2002). Caspase 3 activity is required for skeletal muscle differentiation. P Natl Acad Sci USA 99: 11025–11030.

Fernando P, Megeney LA (2007). Is caspase-dependent apoptosis only cell differentiation taken to the extreme? FASEB J 21: 8–17.

Fink SL, Cookson BT (2005). Apoptosis, pyroptosis and necrosis: mechanistic description of death and dying eukaryotic cells. Infect Immun 73: 1907–1916.

Fischer B, Metzger M, Richardson R, Knyphausen P, Ramezani T, Franzen R, Schmelzer E, Bloch W, Carney TJ, Hammerschmidt M (2014). p53 and TAp63 promote keratinocyte proliferation and differentiation in breeding tubercles of the zebrafish. PLoS Genet 10: e1004048.

Fuchs E, Chen T (2013). A matter of life and death: self-renewal in stem cells. EMBO Rep 14: 39–48.

Fuchs Y, Steller H (2011). Programmed cell death in animal development and disease. Cell 147: 742–758.

Fujita J, Crane AM, Souza MK, Dejosez M, Kyba M, Flavell RA, Thomson JA, Zwaka TP (2008). Caspase activity mediates the differentiation of embryonic stem cells. Cell Stem Cell 2: 595–601.

Fulle S, Sancilio S, Mancinelli R, Gatta V, Di Pietro R (2013). Dual role of the caspase enzymes in satellite cells from aged and young subjects. Cell Death Dis 4: e955.

Galluzzi L, Vitale J, Abrams JM, Alnemri ES, Baehrecke EH, Blagosklonny MV, Dawson TM, Dawson VL, El-Deiry WS, Fulda S et al. (2012). Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death. Cell Death Differ 19: 107–120.

Gdynia G, Grund K, Eckert A, Böck BC, Funke B, Macher-Goeppinger S, Sieber S, Herold-Mende C, Wiestler B, Wiestler OD et al. (2007). Basal caspase activity promotes migration and invasiveness in glioblastoma cells. Mol Cancer Res 5: 1232–1240.

Gezginci S, Bolkent S (2007). The effect of Z-FA.FMK on D-galactosamine/TNF-alpha-induced liver injury in mice. Cell Biochem Funct 25: 277–286.

Gezginci-Oktayoglu S, Bolkent S (2012). Ras signaling in NGF reduction and TNF-α-related pancreatic β cell apoptosis in hyperglycemic rats. Apoptosis 17: 14–24.

Gezginci-Oktayoglu S, Sacan O, Yanardag R, Karatug A, Bolkent S (2011). Exendin-4 improves hepatocyte injury by decreasing proliferation through blocking NGF/TrkA in diabetic mice. Peptides 32: 223–231.

Gezginci-Oktayoglu S, Tunali S, Yanardag R, Bolkent S (2008). Effects of Z-FA.FMK on D-galactosamine/tumor necrosis factor-alpha-induced kidney injury and oxidative stress in mice : effects of Z-FA.FMK on TNF-alpha-mediated kidney injury. Mol Cell Biochem 309: 9–20.

Goessling W, North TE, Loewer S, Lord AM, Lee S, Stoick-Cooper CL, Weidinger G, Puder M, Daley GQ, Moon RT et al. (2009). Genetic interaction of PGE2 and Wnt signaling regulates developmental specification of stem cells and regeneration. Cell 136: 1136–1147.

Golstein P, Kroemer G (2006). Cell death by necrosis: towards a molecular definition. Trends Biochem Sci 32: 37–42.

Gozuacik D, Bialik S, Raveh T, Mitou G, Shohat G, Sabanay H, Mizushima N, Yoshimon T, Kimchi A (2008). DAP-Kinase is a mediator of endoplasmic reticulum stress-induced caspase activation and autophagic cell death. Cell Death Differ 15: 1875–1886.

Gregory CD, Pound JD (2011). Cell death in the neighbourhood: direct microenvironmental effects of apoptosis in normal and neoplastic tissues. J Pathol 223: 177–194.

Gurtner GC, Werner S, Barrandon Y, Longaker MT (2008). Wound repair and regeneration. Nature 453: 314–321.

Hagimoto N, Kuwano K, Miyazaki H, Kunitake R, Fujita M, Kawasaki M, Kaneko Y, Hara N (1997). Induction of apoptosis and pulmonary fibrosis in mice in response to ligation of Fas antigen. Am J Respir Cell Mol Biol 17: 272–278.

Herold S, Tabar TS, Janssen H, Hoegner K, Cabanski M, Lewe Schlosser P, Albrecht J, Driever F, Vadasz I, Seeger W et al. (2011). Exudate macrophages attenuate lung injury by the release of IL-1 receptor antagonist in gram-negative pneumonia. Am J Respir Crit Care Med 183: 1380–1390.

Herz HM, Chen Z, Scherr H, Lackey M, Bolduc C, Bergmann A (2006). vps25 mosaics display non-autonomous cell survival and overgrowth, and autonomous apoptosis. Development 133: 1871–1880.

Hewitson TD (2012). Fibrosis in the kidney: is a problem shared a problem halved? Fibrogenesis Tissue Repair 5 (Suppl. 1): S14.

Huang Q, Li F, Liu X, Li W, Shi W, Liu FF, O'Sullivan B, He Z, Peng Y, Tan AC et al. (2011). Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy. Nat Med 17: 860–866.

Huesmann GR, Clayton DF (2006). Dynamic role of postsynaptic caspase-3 and BIRC4 in zebra finch song-response habituation. Neuron 52: 1061–1072.

Huh JR, Guo M, Hay BA (2004). Compensatory proliferation induced by cell death in the Drosophila wing disc requires activity of the apical cell death caspase Dronc in a nonapoptotic role. Curr Biol 14: 1262–1266.

Ishizaki Y, Jacobson MD, Raff MC (1998). A role for caspases in lens fiber differentiation. J Cell Biol 140: 153–158.

Janzen V, Fleming HE, Riedt T, Karlsson G, Riese MJ, Lo Celso C, Reynolds G, Milne CD, Paige CJ, Karlsson S et al. (2008). Hematopoietic stem cell responsiveness to exogenous signals is limited by caspase-3. Cell Stem Cell 2: 584–594.

Jejurikar SS, Henkelman EA, Cederna PS, Marcelo CL, Urbanchek MG, Kuzon WM Jr (2006). Aging increases the susceptibility of skeletal muscle derived satellite cells to apoptosis. Exp Gerontol 41: 828–836.

Jiao S, Li Z (2011). Non-apoptotic function of BAD and BAX in long-term depression of synaptic transmission. Neuron 70: 758–772.

Jouan-Lanhouet S, Arshad MI, Piquet-Pellorce C, Martin-Chouly C, Le Moigne Muller G, Van Herreweghe F, Takahashi N, Sergent O, Laqadic-Goossman D, Vanderabeele P et al. (2012). TRAIL induces necroptosis involving RIPK1/RIPK3-dependent PARP-1 activation. Cell Death Differ 19: 2003–2014.

Jun JI, Lau LF (2010). Cellular senescence controls fibrosis in wound healing. Aging (Albany NY) 2: 627–631.

Kang TB, Ben-Moshe T, Varfolomeev EE, Pewzner-Jung Y, Yogev N, Jurewicz A, Waisman A, Brenner O, Haffner R, Gustafsson E et al. (2004). Caspase-8 serves both apoptotic and nonapoptotic roles. J Immunol 173: 2976–2984.

Kaplan Y, Gibbs-Bar L, Kalifa Y, Feinstein-Rotkopf Y, Arama E (2010). Gradients of a ubiquitin E3 ligase inhibitor and a caspase inhibitor determine differentiation or death in spermatids. Dev Cell 19: 160–173.

Kataoka T, Tschopp J (2004). N-terminal fragment of c-FLIP(L) processed by caspase 8 specifically interacts with TRAF2 and induces activation of the NF-kappaB signaling pathway. Mol Cell Biol 24: 2627–2636.

Kayagaki N, Warming S, Lamkanfi M, Vande Walle L, Louie S, Dong J, Newton K, Qu Y, Liu J, Heldens S et al. (2011). Non-canonical inflammasome activation targets caspase-11. Nature 479: 117–121.

Kayalar O, Oztay F (2014). Retinoic acid induced repair in the lung of adult hyperoxic mice, reducing transforming growth factor-β1 mediated abnormal alterations. Acta Histochem 116: 810–819.

Kim KW, Hwang M, Moretti L, Jaboin JJ, Cha YI, Lu B (2008). Autophagy upregulation by inhibitors of caspase-3 and mTOR enhances radiotherapy in a mouse model of lung cancer. Autophagy 4: 659–668.

Koizumi K, Saitoh Y, Minami T, Takeno N, Tsuneyama K, Miyahara T, Nakayama T, Sakurai H, Takano Y, Nishimura M et al. (2009). Role of CX3CL1/fractalkine in osteoclast differentiation and bone resorption. J Immunol 183: 7825–7831.

Koleva M, Kappler R, Vogler M, Herwig A, Fulda S, Hahn H (2005). Pleiotropic effects of sonic hedgehog on muscle satellite cells. Cell Mol Life Sci 62: 1863–1870.

Kondo S, Senoo-Matsuda N, Hiromi Y, Miura M (2006). DRONC coordinates cell death and compensatory proliferation. Mol Cell Biol 26: 7258–7268.

Konigshoff M, Kramer M, Balsara N, Wilhelm J, Amarie OV, Jahn A, Rose F, Fink L, Seeger W, Schaefer L et al. (2009). WNT1-inducible signaling protein-1 mediates pulmonary fibrosis in mice and is upregulated in humans with idiopathic pulmonary fibrosis. J Clin Invest 119: 772–787.

Kroemer G, Galluzzi L, Vandenabeele P, Abrams J, Alnemri ES, Baehrecke EH, Blagosklonny MV, El-Deiry WS, Golstein P, Green DR et al. (2009). Classification of cell death: recommendations of the Nomenclature Committee on Cell Death. Cell Death Differ 16: 3–11.

Kulasekaran P, Scavone CA, Rogers DS, Arenberg DA, Thannickal VJ, Horowitz JC (2009). Endothelin-1 and transforming growth factor-beta1 independently induce fibroblast resistance to apoptosis via AKT activation. Am J Respir Cell Mol Biol 41: 484–493.

Kuranaga E, Miura M (2007). Nonapoptotic functions of caspases: caspases as regulatory molecules for immunity and cell-fate determination. Trends Cell Biol 17: 135–144.

Kushner EJ, MacEneaney OJ, Weil BR, Greiner JJ, Stauffer BL, DeSouza CA (2011). Aging is associated with a proapoptotic endothelial progenitor cell phenotype. J Vasc Res 48: 408–414.

Labbé K, Saleh M (2011). Pyroptosis: a caspase-1-dependent programmed cell death and a barrier to infection. In: Couillin I, Pétrilli V, Martinon F, editors. The Inflammasomes. Basel, Switzerland: Springer Basel AG, pp. 17–36.

Larsen BD, Rampalli S, Burns LE, Brunette S, Dilworth FJ, Megeney LA (2010). Caspase 3/caspase-activated DNase promote cell differentiation by inducing DNA strand breaks. P Natl Acad Sci USA 107: 4230–4235.

Lavrik IN, Golks A, Krammer PH (2005). Caspases: pharmacological manipulation of cell death. J Clin Invest 115: 2665–2672.

Lee TV, Ding T, Chen Z, Rajendran V, Scherr H, Lackey M, Bolduc C, Bergmann A (2008). The E1 ubiquitin-activating enzyme Uba1 in *Drosophila* controls apoptosis autonomously and tissue growth nonautonomously. Development 135: 43–52.

Lens SM, Kataoka T, Fortner KA, Tinel A, Ferrero I, MacDonald RH, Hahne M, Beermann F, Attinger A, Orbea HA et al. (2002). The caspase 8 inhibitor c-FLIP(L) modulates T-cell receptor-induced proliferation but not activation-induced cell death of lymphocytes. Mol Cell Biol 22: 5419–5433.

Li F, Huang Q, Chen J, Peng Y, Roop DR, Bedford JS, Li CY (2010). Apoptotic cells activate the "phoenix rising" pathway to promote wound healing and tissue regeneration. Sci Signal 3: ra13.

Li J, Brieher WM, Scimone ML, Kang SJ, Zhu H, Yin H, von Andrian UH, Mitchison T, Yuan J (2007). Caspase-11 regulates cell migration by promoting Aip1-Cofilin-mediated actin depolymerization. Nat Cell Biol 9: 276–286.

Li J, Yuan J (2008). Caspases in apoptosis and beyond. Oncogene 27: 6194–6206.

Li W, Kale A, Baker NE (2009). Oriented cell division as a response to cell death and cell competition. Curr Biol 19: 1821–1826.

Liu L, Nishio N, Ito S, Tanaka Y, Isobe K ( 2014). Negative regulation of GADD34 on myofibroblasts during cutaneous wound healing. Biomed Res Int 2014: 137–149.

Liu X, He Y, Li F, Huang Q, Kato TA, Hall RP, Li CY (2015). Caspase-3 promotes genetic instability and carcinogenesis. Mol Cell 58: 284–296.

Liu YR, Sun B, Zhao XL, Gu Q, Liu ZY, Dong XY, Che N, Mo J (2013). Basal caspase-3 activity promotes migration, invasion, and vasculogenic mimicry formation of melanoma cells. Melanoma Res 23: 243–253.

Lovric MM, Hawkins CJ (2010). TRAIL treatment provokes mutations in surviving cells. Oncogene 29: 5048–5060.

Luo X, Kraus WL (2012). On PAR with PARP: cellular stress signaling through poly (ADP-ribose) and PARP-1. Genes Dev 26: 417–432.

Ma J, Chen T, Mandelin J, Ceponis A, Miller NE, Hukkanen M, Ma GF, Konttinen YT (2003). Regulation of macrophage activation. Cell Mol Life Sci 60: 2334–2346.

Maeda S, Kamata H, Luo JL, Leffert H, Karin M (2005). IKKb couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis. Cell 121: 977–990.

Mao C, Obeid LM (2008). Ceramidases: regulators of cellular responses mediated by ceramide, sphingosine, and sphingosine-1-phosphate. Biochim Biophys Acta 1781: 424–434.

Mao P, Smith L, Xie W, Wang M (2013). Dying endothelial cells stimulate proliferation of malignant glioma cells via a caspase 3-mediated pathway. Oncol Lett 5: 1615–1620.

Marcotte R, Lacelle C, Wang E (2004). Senescent fibroblasts resist apoptosis by downregulating caspase-3. Mech Ageing Dev 125: 777–783.

Martinon F, Tschopp J (2007). Inflammatory caspases and inflammasomes; master switches of inflammation. Cell Death Differ 14: 10–22.

Matalova E, Lesot H, Svandova E, Vanden Berghe T, Sharpe PT, Healy C, Vandenabeele P, Tucker AS (2013). Caspase-7 participates in differentiation of cells forming dental hard tissues. Dev Growth Differ 55: 615–621.

McIlwain DR, Berger T, Mak TW (2013). Caspase functions in cell death and disease. Cold Spring Harb Perspect Biol 5: a008656.

Micheau O, Thome M, Schneider P, Holler N, Tschopp J, Nicholson DW, Briand C, Grütter MG (2002). The long form of FLIP is an activator of caspase-8 at the Fas death-inducing signaling complex. J Biol Chem 277: 45162–45171.

Miura M (2012). Apoptotic and nonapoptotic caspase functions in animal development. Cold Spring Harb Perspect Biol 4: a008664.

Miura M, Chen XD, Allen MR, Bi Y, Gronthos S, Seo BM, Lakhani S, Flavell RA, Feng XH, Robey PG et al. (2004). A crucial role of caspase-3 in osteogenic differentiation of bone marrow stromal stem cells. J Clin Invest 114: 1704–1713.

Moberg KH, Schelble S, Burdick SK, Hariharan IK (2005). Mutations in erupted, the Drosophila ortholog of mammalian tumor susceptibility gene 101, elicit non-cell-autonomous overgrowth. Dev Cell 9: 699–710.

Mogi M, Togari A (2003). Activation of caspases is required for osteoblastic differentiation. J Biol Chem 278: 47477–47482.

Monack DM, Raupach B, Hromockyj AE, Falkow S (1996). *Salmonella typhimurium* invasion induces apoptosis in infected macrophages. P Natl Acad Sci USA 93: 9833–9838.

Moodley YP, Misso NL, Scaffidi AK, Fogel-Petrovic M, McAnulty RJ, Laurent GJ, Thompson PJ, Knight DA (2003). Inverse effects of interleukin-6 on apoptosis of fibroblasts from pulmonary fibrosis and normal lungs. Am J Respir Cell Mol Biol 29: 490–498.

Moretti L, Kim KW, Jung DK, Willey CD, Lu B (2009). Radiosensitization of solid tumors by Z-VAD, a pan-caspase inhibitor. Mol Cancer Ther 8: 1270–1279.

Murray TV, McMahon JM, Howley BA, Stanley A, Ritter T, Mohr A, Zwacka R, Fearnhead HO (2008). A non-apoptotic role for caspase-9 in muscle differentiation. J Cell Sci 121: 3786–3793.

Nikoletopoulou V, Markaki M, Palikaras K, Tavernarakis N (2013). Crosstalk between apoptosis, necrosis and autophagy. Biochim Biophys Acta 1833: 3448–3459.

Norman JM, Cohen GM, Bampton ET (2010). The in vitro cleavage of the hAtg proteins by cell death proteases. Autophagy 6: 1042–1056.

O'Brien LE, Soliman SS, Li X, Bilder D (2011). Altered modes of stem cell division drive adaptive intestinal growth. Cell 147: 603–614.

Oh J, Lee YD, Wagers AJ (2014). Stem cell aging: mechanisms, regulators and therapeutic opportunities. Nat Med 20: 870–880.

Okuyama R, Nguyen BC, Talora C, Ogawa E, Tommasi di Vignano A, Lioumi M, Chiorino G, Tagami H, Woo M, Dotto GP (2004). High commitment of embryonic keratinocytes to terminal differentiation through a Notch1-caspase 3 regulatory mechanism. Dev Cell 6: 551–562.

Olson NE, Graves JD, Shu GL, Ryan EJ, Clark EA (2003). Caspase activity is required for stimulated B lymphocytes to enter the cell cycle. J Immunol 170: 6065–6072.

Oral O, Oz-Arslan D, Itah Z, Naghavi A, Deveci R, Karacali S, Gozuacik D (2012). Cleavage of tg3 protein by caspase-8 regulates autophagy during receptor-activated cell death. Apoptosis 17: 810–820.

Ovet H, Oztay F (2014). The copper chelator tetrathiomolybdate regressed bleomycin-induced pulmonary fibrosis in mice, by reducing lysyl oxidase expressions. Biol Trace Elem Res 162: 189–199.

Oztay F, Gezginci-Oktayoglu S, Bayrak BB, Yanardag R, Bolkent S (2010). Cathepsin B inhibition improves lung injury associated to D-galactosamine/tumor necrosis factor-alpha-induced liver injury in mice. Mol Cell Biochem 333: 65–72.

Oztay F, Yilmaz O (2015). Method of Treating Fibrotic Diseases Using Dasatinib. TR201503969A2.

Pellettieri J, Fitzgerald P, Watanabe S, Mancuso J, Green DR, Sánchez Alvarado A (2010). Cell death and tissue remodeling in planarian regeneration. Dev Biol 338: 76–85.

Pérez-Garijo A, Martín FA, Morata G (2004). Caspase inhibition during apoptosis causes abnormal signalling and developmental aberrations in *Drosophila*. Development 131: 5591–5598.

Pérez-Garijo A, Shlevkov E, Morata G (2009). The role of Dpp and Wg in compensatory proliferation and in the formation of hyperplastic overgrowths caused by apoptotic cells in the *Drosophila* wing disc. Development 136: 1169–1177.

Peter ME, Krammer PH (2003). The CD95 (APO-1/Fas) DISC and beyond. Cell Death Differ 10: 26–35.

Pfleger CM, Harvey KF, Yan H, Hariharan IK (2007). Mutation of the gene encoding the ubiquitin activating enzyme Uba1 causes tissue overgrowth in *Drosophila*. Fly 1: 95–105.

Plenchette S, Cathelin S, Rébé C, Launay S, Ladoire S, Sordet O, Ponnelle T, Debili N, Phan TH, Padua RA et al. (2004). Translocation of the inhibitor of apoptosis protein c-IAP1 from the nucleus to the Golgi in hematopoietic cells undergoing differentiation: a nuclear export signal-mediated event. Blood 104: 2035–2043.

Pop C, Oberst A, Drag M, van Raam BJ, Riedl SJ, Green DR, Salvesen GS (2011). FLIPL induces caspase 8 activity in the absence of interdomain caspase 8 cleavage and alters substrate specificity. Biochem J 433: 447–457.

Ribeil JA, Zermati Y, Vandekerckhove J, Cathelin S, Kersual J, Dussiot M, Coulon S, Moura IC, Zeuner A, Kirkegaard-Sørensen T et al. (2007). Hsp70 regulates erythropoiesis by preventing caspase-3-mediated cleavage of GATA-1. Nature 445: 102–105.

Rudrapatna VA, Bangi E, Cagan RL (2013). Caspase signalling in the absence of apoptosis drives Jnk-dependent invasion. EMBO Rep 14: 172–177.

Ryborg AK, Johansen C, Iversen L, Kragballe K (2004). Lysophosphatidylcholine induces keratinocyte differentiation and upregulation of AP-1- and NF-kappaB DNA-binding activity. Acta Derm Venereol 84: 433–438.

Ryoo HD, Gorenc T, Steller H (2004). Apoptotic cells can induce compensatory cell proliferation through the JNK and the Wingless signaling pathways. Dev Cell 7: 491–501.

Sakurai T, Maeda S, Chang L, Karin M (2006). Loss of hepatic NF-kB activity enhances chemical hepatocarcinogenesis through sustained c-Jun N-terminal kinase 1 activation. P Natl Acad Sci USA 103: 10544–10551.

Salmena L, Lemmers B, Hakem A, Matysiak-Zablocki E, Murakami K, Au PY, Berry DM, Tamblyn L, Shehabeldin A, Migon E et al. (2003). Essential role for caspase 8 in T-cell homeostasis and T-cell-mediated immunity. Genes Dev 17: 883–895.

Santiago B, Galindo M, Palao G, Pablos JL (2004). Intracellular regulation of Fas-induced apoptosis in human fibroblasts by extracellular factors and cycloheximide. J Immunol 172: 560–566.

Schwab JM, Chiang N, Arita M, Serhan CN (2007). Resolvin E1 and protectin D1 activate inflammation-resolution programmes. Nature 447: 869–874.

Senft J, Helfer B, Frisch SM (2007). Caspase-8 interacts with the p85 subunit of phosphatidylinositol 3-kinase to regulate cell adhesion and motility. Cancer Res 67: 11505–11509.

Shalini S, Dorstyn L, Dawar S, Kumar S (2015). Old, new and emerging functions of caspases. Cell Death Differ 22: 526–539.

Shi J, Zhao Y, Wang Y, Gao W, Ding J, Li P, Hu L, Shao F (2014). Inflammatory caspases are innate immune receptors for intracellular LPS. Nature 514: 187–192.

Solá S, Aranha MM, Rodrigues CM (2012). Driving apoptosis-relevant proteins toward neural differentiation. Mol Neurobiol 46: 316–331.

Solá S, Morgado AL, Rodrigues CMP (2013). Death receptors and mitochondria: two prime triggers of neural apoptosis. Biochim Biophys Acta 1830: 2160–2166.

Sollberger G, Strittmatter GE, Garstkiewicz M, Sand J, Beer HD (2014). Caspase-1: the inflammasome and beyond. Innate Immun 20: 115–125.

Sordet O, Rébé C, Plenchette S, Zermati Y, Hermine O, Vainchenker W, Garrido C, Solary E, Dubrez-Daloz L (2002). Specific involvement of caspases in the differentiation of monocytes into macrophages. Blood 100: 4446–4453.

Stoneman V, Bennett MR (2009). Role of Fas/Fas-L in vascular cell apoptosis. J Cardiovasc Pharmacol 53: 100–108.

Su H, Bidère N, Zheng L, Cubre A, Sakai K, Dale J, Salmena L, Hakem R, Straus S, Lenardo M (2005). Requirement for caspase-8 in NF-kappaB activation by antigen receptor. Science 307: 1465–1468.

Tanaka T, Yoshimi M, Maeyama T, Hagimoto N, Kuwano K, Hara N (2002). Resistance to Fas-mediated apoptosis in human lung fibroblast. Eur Respir J 20: 359–368.

Thompson BJ, Mathieu J, Sung HH, Loeser E, Rørth P, Cohen SM (2005). Tumor suppressor properties of the ESCRT-II complex component Vps25 in *Drosophila*. Dev Cell 9: 711–720.

Tiwari M, Sharma LK, Vanegas D, Callaway DA, Bai Y, Lechleiter JD, Herman B (2014). A nonapoptotic role for CASP2/caspase 2: modulation of autophagy. Autophagy 10: 1054–1070.

Tschopp J, Irmler M, Thome M (1998). Inhibition of fas death signals by FLIPs. Curr Opin Immunol 10: 552–558.

Uhal BD, Joshi I, Hughes WF, Ramos C, Pardo A, Selman M (1998). Alveolar epithelial cell death adjacent to underlying myofibroblasts in advanced fibrotic human lung. Am J Physiol-Lung C 275: L1192–L1199.

Uhal BD, Joshi I, True AL, Mundle S, Raza A, Pardo A, Selman M (1995). Fibroblasts isolated after fibrotic lung injury induce apoptosis of alveolar epithelial cells in vitro. Am J Physiol-Lung C 269: L819–L828.

Vaccari T, Bilder D (2005). The *Drosophila* tumor suppressor vps25 prevents nonautonomous overproliferation by regulating notch trafficking. Dev Cell 9: 687–698.

Vandenabeele P, Galluzzi L, Vanden Berghe T, Kroemer G (2010). Molecular mechanisms of necroptosis: an ordered cellular explosion. Nat Rev Mol Cell Biol. 11: 700–714.

Vercammen BD, Beyaert R, Denecker G, Goossens V, Loo GV, Declercq W, Grooten J, Fiers W, Vanderabeele P (1998). Inhibition of caspases increases the sensitivity of L929 cells to necrosis mediated by tumor necrosis factor. J Exp Med 187: 1477–1485.

Viganò E, Mortellaro A (2013). Caspase-11: the driving factor for nancanonical inflammasomes. Eur J Immunol 43: 2240–2245.

Wang R, Ramos C, Joshi I, Zagariya A, Pardo A, Selman M, Uhal BD (1999). Human lung myofibroblast-derived inducers of alveolar epithelial apoptosis identified as angiotensin peptides. Am J Physiol 277: L1158–L1164.

Watt FM, Estrach S, Ambler CA (2008). Epidermal Notch signalling: differentiation, cancer and adhesion. Curr Opin Cell Biol 20: 171–179.

Wilson A, Shehadeh LA, Yu H, Webster KA (2010). Age-related molecular genetic changes of murine bone marrow mesenchymal stem cells. BMC Genomics 11: 229.

Woo M, Hakem R, Furlonger C, Hakem A, Duncan GS, Sasaki T, Bouchard D, Lu L, Wu GE, Paige CJ et al. (2003). Caspase-3 regulates cell cycle in B cells: a consequence of substrate specificity. Nat Immunol 4: 1016–1022.

Wu H, Che X, Zheng Q, Wu A, Pan K, Shao A, Wu Q, Zhang J, Hong Y (2014). Caspases: a molecular switch node in the crosstalk between autophagy and apoptosis. Int J Biol Sci 10: 1072–1083.

Yan XX, Najbauer J, Woo CC, Dashtipour K, Ribak CE, Leon M (2001). Expression of active caspase-3 in mitotic and postmitotic cells of the rat forebrain. J Comp Neurol 433: 4–22.

Yang L, Cao Z, Yan H, Wood WC (2003). Coexistence of high levels of apoptotic signaling and inhibitor of apoptosis proteins in human tumor cells: implication for cancer specific therapy. Cancer Res 63: 6815–6524.

Yi CH, Yuan J (2009). The Jekyll and Hyde functions of caspases. Dev Cell 16: 21–34.

Zermati Y, Garrido C, Amsellem S, Fishelson S, Bouscary D, Valensi F, Varet B, Solary E, Hermine O (2001). Caspase activation is required for terminal erythroid differentiation. J Exp Med 193: 247–254.

Zhao X, Wang D, Zhao Z, Xiao Y, Sengupta S, Xiao Y, Zhang R, Lauber K, Wesselborg S, Feng L et al. (2006). Caspase-3-dependent activation of calcium-independent phospholipase A2 enhances cell migration in non-apoptotic ovarian cancer cells. J Biol Chem 281: 29357–29368.

Zhong Z, Schwabe RF, Kai Y, He L, Yang L, Bunzendahl H, Brenner DA, Lemasters JJ (2006). Liver regeneration is suppressed in small-for-size liver grafts after transplantation: involvement of c-Jun N-terminal kinase, cyclin D1, and defective energy supply. Transplantation 82: 241–250.