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Minireview

Molecular control of neutrophil apoptosis

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Abstract Human neutrophils constitutively undergo apoptosis and this process is critical for the resolution of inflammation. Whilst neutrophil apoptosis can be modulated by a wide variety of agents including GM-CSF, LPS and TNF-α, the molecular mechanisms underlying neutrophil death and survival remain largely undefined. Recent studies have shown the involvement of members of the Bcl-2 protein family (especially Mcl-1 and A1) and caspases in the regulation and execution of neutrophil apoptosis. Cell surface receptors and protein kinases, particularly mitogen-activated protein kinases, also play critical roles in transducing the signals that result in neutrophil apoptosis or extended survival. This review summarises current knowledge on the molecular mechanisms and components of neutrophil apoptosis.

Key words: Bcl-2 family; Caspase; Protein kinase; Mitogen-activated protein kinase; Mcl-1; A1

1. Introduction

Neutrophils are polymorphonuclear leukocytes that are essential components of the natural immune system. They form the first line of defence against bacterial and fungal infections. Neutrophils are terminally differentiated cells and are produced in the bone marrow from myeloid stem cells by the process called 'phagocytopoiesis'. Whilst they have a very short half life in the circulation (8–20 h), this can increase several fold once they enter infected or inflamed tissues [1]. Aged neutrophils undergo spontaneous apoptosis (programmed cell death) in the absence of cytokines or other proinflammatory agents prior to their removal by macrophages [2]. This phagocytic removal of intact, apoptotic neutrophils prevents them from releasing their cytotoxic content into the extracellular milieu that would occur if the cells died by necrosis. In acute inflammation, neutrophil numbers within tissues can be extremely high because of targeted influx from the circulation and because their constitutive apoptotic pathway is delayed by the action of local inflammatory mediators [3]. Thus, the potential for inflammatory neutrophils to cause tissue damage via the release of toxic reactive oxygen species and granule enzymes such as proteases is very high. Death by apoptosis and safe removal by phagocytic cells thus helps to limit tissue damage during the resolution of inflammation. Understanding the processes that regulate constitutive neutrophil apoptosis and cytokine-mediated delay of cell death will lead to a better understanding of the molecular pathology of inflammatory diseases in which neutrophil apoptosis may be perturbed and could also identify new therapeutic targets.

2. Molecular changes in neutrophils during apoptosis

Neutrophils lose their functional properties during apoptosis and they display morphological and biochemical characteristics of an apoptotic cell, including cell shrinkage, compaction of chromatin and loss of the multilobed shape of the nucleus [4–6]. They also show molecular alterations on their cell surface that result from either decreased expression of certain receptors or else the appearance of new surface molecules. Neutrophil apoptosis is accompanied by the down-regulation of the immunoglobulin superfamily members (e.g. CD31, CD50, CD66acde, CD66b, CD63 and CD87) and cell surface receptors (e.g. CD15, CD16, CD32, CD35, CD88, CD120b [8,9]). Phosphatidylserine, a molecular marker of apoptotic cells, also appears on the surface of apoptotic neutrophils as the symmetry of their plasma membrane phospholipids is altered [9,10]. The externalisation of this molecule facilitates the recognition of apoptotic neutrophils by macrophages and it is also a convenient indicator of apoptotic neutrophils as phosphatidylserine can bind fluorescently labelled annexin V [11].

Apoptotic neutrophils are non-functional and lose the ability to move by chemotaxis, generate a respiratory burst or degranulate. This loss of functional capacity results from the disablement of their activation pathways, and the decreased expression of surface receptors aids in this shutdown in activity by preventing them efficiently binding extracellular ligands. These inactive neutrophils, with altered surface epitopes, are then phagocytosed [4,5]. Fibroblasts ingesting apoptotic neutrophils employ both $\alpha_v\beta_3$ and lectin-like receptors, which may recognise the changes in the carbohydrate moieties on the surface of apoptotic cells. The phagocyte adhesion molecule CD36 co-operates with $\alpha_v\beta_3$ to bind thrombospondin (TSP) that is secreted by phagocytes. TSP may function as a bridge between the phagocyte receptors and unknown structures on the surface of apoptotic neutrophils.

The two key questions that need to be addressed are: 'what processes control this high rate of constitutive neutrophil ap-

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Abbreviations: PI3K, phosphoinositide 3-kinase; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-related protein kinase

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optosis?' and 'how is this constitutive apoptotic pathway regulated by external factors?'

3. Extracellular modulators of neutrophil apoptosis and survival

A number of in vitro studies have demonstrated that several factors can accelerate or suppress neutrophil apoptosis. It has been reported that inflammatory cytokines including IL-1β, IL-2, TNF-α, IL-15, INF-γ, G-CSF, GM-CSF and LPS can prolong neutrophil survival [1–18]. The reported effects of IL-6 on neutrophil apoptosis are variable [19,20]. IL-8, a chemokine, has also been shown to delay neutrophil apoptosis mediated by Fas and TNF-α receptors [21,22]. Neutrophils are susceptible to Fas-induced apoptosis and an interaction between Fas and Fas ligand (FasL) was originally suggested to represent a mechanism to explain constitutive neutrophil apoptosis [23]. Neutrophils express significant levels of Fas and whilst early reports indicated that they could also express FasL [23], this finding has not been confirmed in later reports [24,25]. Neutrophils from CD95 deficient mice (lacking Fas) undergo constitutive or spontaneous apoptosis at the same rate as control mice, arguing against a role for the Fas system in constitutive apoptosis [26,27]. In addition, only aggregated or membrane bound FasL, rather than soluble (S)FasL, can induce apoptosis. Recently, SFasL has also been reported to induce neutrophil chemotaxis, rather than apoptosis [28]. Hence, the role of the Fas/FasL system in regulation of neutrophil apoptosis in inflammation and disease is still controversial.

TNF-α has been variably reported to induce, delay or have no effect on neutrophil apoptosis. It has been shown that while prolonged incubations (>12 h) of human neutrophils with TNF-α can cause a decrease in apoptosis, TNF-α can also induce apoptosis in a sub-population of cells at earlier times of incubation (<8 h) [29]. TNF-α may thus rapidly activate a death pathway in susceptible cells, but stimulate an anti-apoptotic pathway in the surviving cells (see later).

It has also been shown that signals triggered in neutrophils via ligation of their adhesion receptors can modify their lifespan [30]. Similarly, a role of endothelial transmigration in the regulation of neutrophil apoptosis has been reported again indicating that adhesion molecules can generate intracellular signals that trigger enhanced survival of neutrophils as they migrate from the bloodstream into tissues [31].

In contrast to observations in other cell types, hypoxia delays apoptosis in human neutrophils [32]. Furthermore, some antioxidants (e.g. catalase) but not others (e.g. superoxide dismutase) can delay apoptosis when neutrophils are incubated under normoxic conditions. In addition, neutrophils from patients with chronic granulomatous disease (which have an impaired capacity to generate reactive oxygen metabolites because of a defect in their NADPH oxidase) have delayed apoptosis in vitro [33]. Thus, exogenous or neutrophil-derived oxidants can promote neutrophil apoptosis. This phenomenon may be important in the function of these cells during inflammation. When recruited into tissues, neutrophils move from normoxic to hypoxic conditions, and hence decreased O_2 tensions at inflammatory sites may extend their life-span. However, if they are activated to secrete large quantities of reactive oxygen metabolites then this may promote their apoptosis and subsequent removal by other professional phagocytes.

Cycloheximide and actinomycin D (inhibitors of translation and transcription, respectively) both accelerate neutrophil apoptosis in vitro [34,35]. This observation, together with the finding that agents that delay neutrophil apoptosis (e.g. cytokines and glucocorticoids such as dexamethasone, [36]) invariably also stimulate protein biosynthesis, leads to the conclusion that neutrophil survival may be regulated by the expression of transiently expressed protein(s). Thus, agents that regulate neutrophil death and survival may do so by altering the activity of pre-existing proteins (e.g. via phosphorylation reactions) or may regulate signalling pathways that lead to the activation of specific transcription factors that induce the expression of key genes.

4. Regulation of neutrophil apoptosis and survival

As is the case in many other cell types, the execution of the apoptotic pathway in neutrophils is mediated by the caspases. Neutrophils have been reported to express a variety of regulatory and effector caspases, including caspases-1, -3, -4 and -8

Table 1
Expression of Bcl-2 family proteins in human neutrophils

Ref.	Bcl-2	Bcl-X_L	Mcl-1	A1	Bcl-w	Bax	Bad	Bak	Bik
[38]	− (R)	− (R)		+ (R)	+ (R)	− (R)	+ (R)	+ (R)	− (R)
[59]	− (R)	+ (R)				+ (R)		+ (R)	
		+ (W)				+ (W)		− (W)	
[60]	− (W)	− (W)	− (W)			+ (W)			
[6]	− (W)	− (W)	+ (W)			+ (W)			
[61]								+ (I)	
[62]	+ (F)								
[63]	− (F)					+ (F)			
[64]							+ (I)		
[55]			+ (RP)	+ (N,RP)					
[65]								+ (N,W)	
[66]	− (F)	+ (F)				+ (F, W)[a]			
						− (F, W)[b]			
[67]			+ (W)						
[68]			+ (W)						

− represents no reported expression, whilst + represents expression. The detection methods are as follows: R, RT-PCR; W, Western blotting; F, flow cytometry; RP, RNase protection; I, immuno-fluorescence; N, Northern blotting.
[a]Expression reported in control neutrophils.
[b]Expression reported in inflammatory neutrophils.

[37,38]. Neutrophils also express a number of the Bcl-2 family of proteins (Table 1), but there are some discrepancies and ambiguities in the literature, largely because of the use of a variety of different methods to detect expression. It is now generally agreed that human neutrophils do not express the anti-apoptotic protein Bcl-2 but they constitutively express the pro-apoptotic proteins Bax, Bid, Bak and Bad. These proteins have a relatively long half life and hence their constitutive expression helps explain why bloodstream neutrophils have such a short survival time in the absence of Bcl-2 expression.

Human neutrophils do express mRNA for the anti-apoptotic proteins, Mcl-1, A1 and Bcl-X_L, but only convincing evidence for the expression of Mcl-1 protein has been obtained [6]. No antibodies are yet available that can reliably detect human A1 protein and expression of Bcl-X_L protein is debated. Mcl-1 protein is expressed in bloodstream neutrophils and its levels decrease prior to the onset of apoptosis [6]. Treatment of neutrophils with agents that delay apoptosis either increases or maintains Mcl-1 levels, providing a mechanism to explain cytokine-mediated increased survival via enhanced expression of an anti-apoptotic protein. Mcl-1 mRNA and protein (and A1 mRNA) have very short half lives (approximately 2–3 h, unpublished) whereas the half lives of the pro-apoptotic proteins are relatively long. Hence, neutrophil apoptosis may be governed by the cellular levels of the relatively short-lived survival proteins, Mcl-1 and A1. In the absence of de novo synthesis of Mcl-1 and A1, the activity of the longer lived pro-apoptotic proteins will predominate and apoptosis will ensue. However, in the presence of survival signals (e.g. cytokines) the enhanced expression of the anti-apoptotic proteins will ensure survival.

It is thus necessary to identify the intracellular signalling pathways that control expression of A1 and Mcl-1 and to determine if the expression of these two survival proteins is controlled by separate or overlapping signalling systems. If transcription of A1 and Mcl-1 is regulated by separate mechanisms, then the possibility exists for the expression of these two survival proteins to be modulated by different extracellular signals under different patho-physiological conditions.

5. Signalling pathways leading to neutrophil apoptosis

In spite of the fact that it has been realised for many years that cytokines and other agents can modulate neutrophil apoptosis, the intracellular signalling pathways that control this process are still largely unknown (Fig. 1). It is clear that phosphorylation cascades, involving phosphorylation on tyrosine, serine and threonine residues, may be important. Agents that elevate cAMP levels delay apoptosis in neutrophils via protein kinase A activity [39] and protein kinase C (PKC) activity, in particular PKC-δ, has also been implicated in constitutive apoptosis of neutrophils [40]. However, the downstream targets of these kinases have not been fully identified.

It has been demonstrated that GM-CSF, TNF-α and LPS increase the tyrosine phosphorylation of a number of proteins, including the isoforms of mitogen-activated protein kinases (MAPKs) [41,42]. MAPKs are extracellular signal-regulated protein kinases that are important mediators of signal transduction pathways regulated by many types of cell surface receptors. Phosphorylation of proteins on tyrosine residues, including activation of MAPK, may thus be important in controlling the activation of the various neutrophil processes

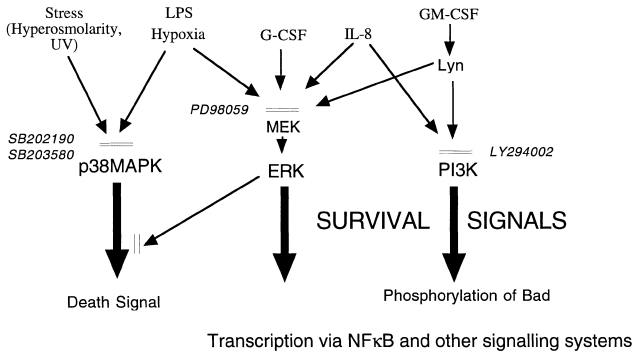

Fig. 1. Possible roles of MAPKs and PI3K in neutrophil apoptosis and survival. Acceleration of neutrophil apoptosis, e.g. via stress, may involve the generation of death signals via the activity of p38MAPK. In the presence of survival signals (e.g. cytokines or LPS) p38MAPK kinase may still be active, but signals generated via activated ERK and PI3K may override or inhibit the p38MAPK death signal, and so neutrophil apoptosis is delayed. It has, however, been reported that hypoxia-mediated activation of p38MAPK may result in the generation of a survival signal [45]. The survival signals may include phosphorylation (e.g. inactivation of Bad), and/or activation of transcription factors that up-regulate expression of the survival proteins, A1 and Mcl-1. Other signalling pathways and intermediary components of these signalling systems are likely to exist. Sites of action of inhibitors used to probe function are shown in italics.

required for their function in host defence, but may also be important in the pathways regulating neutrophil cell death and survival.

There are three major types of MAPKs in mammalian cells: p42/44 extracellular signal-related protein kinase (ERK) (which are activated by phosphorylated MEK), p38MAPK and c-Jun N-terminal kinase/stress-activated MAPK (which are generally activated by stresses, such as irradiation and hyperosmolarity). Whilst all three types of MAPK have been detected in human neutrophils, supporting evidence (generally via detection of the active forms of these kinases using antibodies that only bind the phosphorylated proteins in Western blots) for only ERK and p38MAPK in neutrophil apoptosis has been reported. Additionally, the functional role of these kinases can be probed with the use of inhibitors: PD98059 (which inhibits MEK, thereby preventing the phosphorylation and activation of ERK), and SB902190 and SB203580 which are used to inhibit p38MAPK.

There has been much interest in the role of p38MAPK in the regulation of neutrophil apoptosis and survival. Whilst experiments using inhibitors and antisense technology indicated a role for p38MAPK in constitutive apoptosis of neutrophils [43], this finding has not been confirmed in other reports [27,44]. Cellular stresses (such as hyperosmolarity or irradiation) clearly stimulated p38MAPK activity and accelerated apoptosis [44]. However, some factors that either delayed (GM-CSF) or accelerated apoptosis (anti-Fas antibodies) have been reported not to affect the activation status of p38MAPK [43]. The role of p38MAPK is further complicated by the report that hypoxia-mediated delay of apoptosis requires p38MAPK activity [45] whereas LPS delayed apoptosis is enhanced when p38MAPK activity is inhibited [46]. The

role of p38MAPK in the control of neutrophil apoptosis and survival is therefore unclear. Perhaps divergent signals generated downstream of p38MAPK activation can control either cell death or survival or perhaps survival signals generated from other systems (e.g. ERK, see below) can modulate the death signal generated by p38MAPK (Fig. 1).

Clear evidence is emerging that ERK activity results in the generation of survival signals. GM-CSF has been shown to increase the activity of ERK and to delay apoptosis [47], presumably via activation of Lyn kinase [48]. Furthermore, apoptosis delaying agents (such as GM-CSF and IL-8) can additionally activate phosphoinositide 3-kinase (PI3K) [47] and this activation is also associated with the generation of survival signals that can override the p38MAPK death signals [44]. However, the survival signals generated by PI3K may be different to those generated by ERK. PI3K can activate (phosphorylate) Akt, which in turn may phosphorylate Bad, thereby decreasing its pro-apoptotic effects [47].

This multiplicity of the pro- and anti-apoptotic signals generated by activated MAPKs may also help explain the differential effects of cytokines on neutrophil survival. For example, G-CSF was shown to strongly activate ERK (via MEK) whereas GM-CSF strongly activated ERK and but only weakly activated p38MAPK [49]. These cytokines will thus both generate survival signals. These MAPKs may also be responsible, at least in part, for the inhibition of constitutive apoptosis seen during incubation under hypoxia. Experiments using PD98059 and SB202190 showed that ERK and p38MAPK, respectively, were involved in regulating hypoxia-mediated delay of apoptosis [45]. This delay of apoptosis was associated with increased expression of the survival protein, Mcl-1, which suggests that hypoxia-induced expression of this protein is regulated by the activity of these kinases.

The effects of TNF on neutrophils are complicated by the fact that this agent rapidly accelerates apoptosis in a sub-population of cells, but generates an anti-apoptotic signal in the remaining cells [29]. TNF-α was shown to strongly activate p38MAPK [49] which may generate a death signal in the sub-population of neutrophils that are susceptible to this agent. It must also be pointed out that ligation of TNF-α with its receptor can activate caspase-8, which in turn activates a caspase cascade that can also generate strong death signals [50,51]. In contrast, the survival signals generated by TNF-α in the sub-population of neutrophils that are not initially killed by this cytokine may be mediated via enhanced transcription of survival proteins via activation of the transcription factor, NFκB [52]. Thus, under certain circumstances, NFκB-regulated gene products may be important in cytokine-mediated neutrophil survival [53].

A1 has been shown to be a gene whose expression is regulated by NFκB in other cell systems [54]. A1 mRNA is constitutively expressed in human neutrophils and its expression can be further enhanced by GM-CSF, LPS and TNF-α and by phagocytic stimuli [55]. However, not all agents that delay neutrophil apoptosis can activate NFκB [52,56]. Indeed, GM-CSF, which is a potent delayer of neutrophil apoptosis, does not generate signals leading to NFκB activation. Furthermore, whilst the *A1* gene has clearly identifiable consensus NFκB binding motifs [57], the human *mcl-1* gene does not appear to be regulated by NFκB [58]. Clearly, in human neutrophils, there appear to be NFκB-dependent and -independent signalling pathways leading to delay of apoptosis via activated gene expression.

6. Concluding remarks

The high rate of constitutive apoptosis that is a special feature of human neutrophils may be explained, at least in part, by the constitutive expression of a range of pro-apoptotic proteins of the Bcl-2 family. Extended survival that is mediated by cytokines or other exogenous factors appears to involve the inducible expression of the survival proteins A1 and Mcl-1, via pathways that involve activated transcription. Promoter studies indicate that separate transcriptional signalling pathways that involve NFκB and MAPKs regulate the expression of these two proteins. This raises the possibility that these signalling pathways may be independently regulated by different exogenous signals. It will therefore be an important challenge to identify the signalling systems that are activated in diseases in which neutrophil apoptosis and survival are intimately involved in pathology.

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