Biochimica et Biophysica Acta 1822 (2012) 1358–1362

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Peroxisomes, cell senescence, and rates of aging ☆

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ARTICLE INFO

Article history:
Received 10 February 2012
Received in revised form 2 March 2012
Accepted 22 March 2012
Available online 29 March 2012

Keywords:
Peroxisome
Senescence
Aging
Catalase
Reactive oxygen species
Degenerative disease

ABSTRACT

The peroxisome is functionally integrated into an exquisitely complex network of communicating endomembranes which is only beginning to be appreciated. Despite great advances in identifying essential components and characterizing molecular mechanisms associated with the organelle's biogenesis and function, there is a large gap in our understanding of how peroxisomes are incorporated into metabolic pathways and subcellular communication networks, how they contribute to cellular aging, and where their influence is manifested on the initiation and progression of degenerative disease. In this review, we summarize recent evidence pointing to the organelle as an important regulator of cellular redox balance with potentially far-reaching effects on cell aging and the genesis of human disease. The roles of the organelle in lipid homeostasis, anaplerotic reactions, and other critical metabolic and biochemical processes are addressed elsewhere in this volume. This article is part of a Special Issue entitled: Metabolic Functions and Biogenesis of Peroxisomes in Health and Disease.

1. Introduction

The role of cellular senescence in organismal aging bursts into our collective consciousness this past fall with the publication of a paper by Dr. Jan Van Deursen and colleagues at the Mayo Clinic College of Medicine in Rochester, Minnesota. In their landmark work, the team showed that eliminating senescent cells in a mouse model delayed appearance of age-related disorders [1]. Importantly, the strategy was effective both when clearance was started from birth, as well as when initiated later in life. However, in the latter case, already existing pathologies were not reversed, rather their progression was thwarted. In many ways, this research serves as the ultimate confirmation of what many had long speculated — that senescent cells amass in tissues and organs of aging animals and contribute to their physiological decline. What a long way the field had come from days when cellular senescence was considered an in vitro phenomenon, not applicable to the whole animal. In fact, it is only some six years since Dr. John Sedivy and colleagues at Brown University in Providence, Rhode Island, confirmed the existence of senescent cells in the tissue of aging primates [2].

A considerable literature exists concerning exactly what cellular senescence is (for example, see [3] for a detailed and current review); therefore, the phenomena will only be briefly described here. Senescent cells have lost their ability to replicate, yet remain metabolically active. The cells are enlarged and express so-called senescence markers, including an alkaline β-galactosidase activity, heterochromatin and/or DNA damage foci, and the cyclin-dependent kinase inhibitor/tumor suppressor, $p16^{Ink4a}$. (Eradication of (senescent) cells expressing the latter biomarker was the mechanism employed by the Van Deursen group to largely eliminate diseases of aging in mice.) Senescent cells are resistant to apoptosis and exhibit a distinct "secretory phenotype" (reviewed in [4]). They secrete a number of bioactive molecules, including cytokines, growth factors, inflammatory mediators, and various proteases. Secretion of these molecules undoubtedly alters the cell and tissue microenvironments with potentially important implications on aging and disease phenomena. Indeed, there is an emergent consensus view, articulated by Dr. Manuel Collado and co-authors [5] among others, that tissue aging results from the combined effects of an accumulation of senescent cells and accompanying secretions, and the loss of stem cell renewal capacities.[1]

Triggers of replicative senescence include telomere shortening, accumulation of reactive oxygen species and associated damage to cellular macromolecules, DNA alterations and accompanying responses, a loss of cell cycle checkpoint regulation, and the effects of environmental or intrinsic stressors including oncogenes. Importantly, these activators do not necessarily act alone; rather, they may cooperate to elicit the growth stasis and accompanying cellular changes associated with the senescent phenotype.

Is there a reason senescence happens? A widely supported view is that senescence exists to suppress tumor formation; cells that are incapable of dividing cannot contribute to cancer — at least not directly. But as Dr. Judith Campisi [6] and others argue, senescence

☆ This article is part of a Special Issue entitled: Metabolic Functions and Biogenesis of Peroxisomes in Health and Disease.

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[1] The extent to which stem cells actually senesce is not clear; regardless, their diminished function certainly compromises tissue integrity.

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doi:10.1016/j.bbadis.2012.03.013

may be antagonistically pleiotropic — beneficial in early life to thwart cancer, but permissive of an environment later in life which potentiates transformation. Consider the senescent cell's tissue milieu; rich in growth-promoting secreted biomolecules, rich in oxidants, and rich in functionally compromised stem cells. This is an environment ripe for cancerous transformation. Thus, the thought is cancer is held in check early, but may thrive later. Consistent with this notion is the fact that cancer is a disease of aging — the older the individual, the more likely is tumorigenesis.

2. Peroxisomes

2.1. Overview of biogenesis

To be able to position peroxisomes as players in cellular aging processes, an overview of their assembly and function is warranted.

Peroxisome biogenesis is brought about by a series of proteins termed peroxins (see [7,8] for recent analyses). The organelle's membrane is derived by growth and division of pre-existing peroxisomes [9], as well as by recruitment from certain endoplasmic reticulum subdomains [10]. Peroxisomal enzymes, synthesized on cytoplasmic ribosomes and containing specific targeting signals, are recognized post-translationally and directed to the organelle's membrane. A surface-associated docking complex then engages the to-be-imported enzyme and its cognate receptor, and channels the complex to a still rather enigmatic translocation machinery. Mechanisms exist to recycle components of the import apparatus as well as to regulate luminal enzyme levels, and organelle number.

2.2. Overview of biological functions

Peroxisomes are critical contributors to cell metabolism, tissue and organ function, and organismal well-being. They house dozens of enzymes involved in biosynthetic reactions (reviewed in [11,12]), including those that produce ether phospholipids, as well as bile and docosahexaenoic acids. Among the ether phospholipids produced are plasmalogens, essential constituents of myelin, the nerve process insulating material. Bile acids are well described participants in dietary fat metabolism; docosahexaenoic acids are omega-3 fatty acids essential for nervous system development and function. The latter molecules also appear to be derivatized into important mediators capable of inflammatory-suppression/modulation.

Peroxisomes also affect inflammation through their ability to degrade eicosanoids, signaling molecules with a wide array of biological targets and elicited effects. Peroxisomal enzymes degrade a number of other substrates including particular long-chain, very-long-chain, and branched-chain fatty acids. Defects in such processing result in accumulation of these molecules and, in many cases, disease and even death ensue. Metabolism of peroxisomal fatty acids occurs through biochemical oxidations; molecular oxygen is the electron acceptor and hydrogen peroxide is formed (see [13] for an overview of peroxisomes as oxidative organelles). This hydrogen peroxide and related downstream reactive oxygen species appear to play important roles in cell signaling and communication networks, in hormetic processes, as well as in initiating and progressing age-related declines in cell function (reviewed in [14]).

2.3. Contribution to cellular reactive oxygen species levels

Peroxisomal hydrogen peroxide is subject to metabolism by organellar catalase, members of the peroxiredoxin family, and glutathione peroxidase (presumably in some combination with reduced glutathione and a reductase). As catalase is the most abundant and efficient hydrogen peroxide metabolizer, most discussions about peroxisomal antioxidant capacities focus on the heme-containing tetrameric enzyme.

3. Catalase

3.1. Overview of the antioxidant enzyme

There exist individuals whose catalase levels are reduced due to instability of the protein or its mRNA; cells from these subjects display an accelerated aging phenotype [15]. They amass hydrogen peroxide, possess elevated levels of oxidized proteins and damaged DNA, contain functionally compromised peroxisomes and exhibit a growth stasis. Coupled with their altered, largely swollen and amorphous phenotypes, these cells could very well be described as senescent except that they do not express the histochemical biomarker, senescent-associated β-galactosidase [15]. Similar progeric effects are seen in cells where catalase is deactivated with the irreversible inhibitor, 3-amino-1,2,4-triazole [16]. Coupled with powerful epidemiological evidence suggesting that the absence of cellular catalase is directly correlated with premature onset of age-related disease [17,18] — a strong case emerges for a critical role of the enzyme in preventing oxidative stress in cells.

3.2. Catalase, lifespan, and rate of aging

Catalase received very high profile attention when studies published by Dr. Samuel Schriner and co-authors [19,20] showed that transgenic mice expressing catalase in mitochondria manifest a 20% increase in median lifespan and a 10% extension of maximum lifespan. (Peroxisomally targeted catalase showed a more muted effect, which may stem from how the molecule was directed to the organelle — a point considered further below.) Mitochondrial catalase delayed aging phenomena in the heart and eyes, reduced hydrogen peroxide levels in cells, and decreased mitochondrial DNA damage while maintaining mitochondrial function. Fitting these results into a simple model is somewhat problematic [21], however, it is probably safe to conclude, as the authors do [19,20], that reduced cellular oxidative stress positively impacts longevity. Another important conclusion drawn from their studies was that mitochondria were now seen as both sources of reactive oxygen species, and targets of their destructive power.

More recent studies with these mice confirmed that age-associated declines in mitochondrial integrity and function were slowed, but also that (muscle) insulin sensitivity and lipid content were maintained at more youthful levels [22]. Based on their important findings, the authors speculated that mitochondrial reactive oxygen species damage the organelle and potentiate insulin resistance in the animals — leading ultimately to downstream pathologies including a type 2 diabetes phenotype.

As important as all of this is, we should not lose sight of the fact that normally, catalase is not found in the mitochondria — it is a peroxisomal enzyme. Perhaps, in future work, mechanisms could be developed to direct newly introduced/suitably expressed catalase, or an appropriate mimetic, to mitochondria. However, we are a long way off from this at present. What we are closer to, is understanding that a redox-sensitive interplay exists between mitochondria and peroxisomes — one that catalase may play a very important part of. Moreover, unlike mitochondria, peroxisomes may very well be druggable targets in a way mitochondria cannot. The reader is directed to [23] for further analysis of this latter point. Additional discussion of the peroxisome-mitochondria connection is included below — after a brief description of an important study linking catalase, caloric restriction, and longevity.

As a critical antioxidant and one of the most efficient enzymes ever described, catalase has had its share of attention from the aging field. Studies have documented that catalase levels decline with age but are maintained or elevated in more long-lived species. One particularly interesting recent study, headed by Dr. Shugo Watabe, looked at the effects of caloric restriction in the freshwater animal, the rotifer (*Brachionus plicatilis*) [24]. Rotifers live, on average, some 8.8 days. Calorically restricted animals live 13.5 — an approximately

50% increase in lifespan. Rotifers are parthenogenic zooplankton; they reproduce by an asexual process in which daughters are genetically identical to their mothers. The research team asked what happened to offspring of ad libitum-fed animals, versus those subjected to a restricted diet. Not unexpectedly, animals from fed mothers displayed a typical (~9.5 day) lifespan, which could be extended to 14.4 days by a calorie limited diet. Interestingly, offspring from calorically restricted mothers lived 12.7 days when not nutritionally limited, and 16.8 days when the diet was modified. A lifespan enhancing trait was transmitted, presumably by an epigenetic process, to otherwise genetically identical offspring.

Dr. Watabe and colleagues identified that activity — it was catalase [24]. The antioxidant enzyme was expressed at higher levels in offspring of calorically restricted mothers. Manganese superoxide dismutase, a powerful mitochondrial antioxidant enzyme, showed no such behavior. Does the increased catalase activity protect the organism from oxidative stress and contribute to its longevity? The overwhelming conclusion of this study was that it absolutely does. Two final points regarding this work are identified; first, the research is of interest not only from a rate of aging perspective, but it also provides evidence of "transgenerational plasticity" with its accompanying "adaptive" potential [24]. Second, regarding catalase and caloric restriction; this work confirms and extends what has already been shown in a number of model organisms. Specifically, levels of the enzyme are increased in cells of animals whose caloric intake is limited.

3.3. Catalase supplementation and a peroxisome–mitochondria redox interplay

Catalase is progressively mislocalized (to the cytosol) as cells age and approach replicative senescence [25,26]. Concomitantly, these cells produce reactive oxygen species, manifest an ever more compromised peroxisomal import apparatus, and proliferate the organelle in an apparent attempt to compensate for functional shortfalls.[2] As pointed out above, these same phenomena are seen when catalase is missing due to protein or message instabilities, or when the enzyme is chemically inactivated [15,16]. Importantly, restoration of peroxisomal catalase through use of a genetically engineered variant of the enzyme, called catalase-SKL, delays appearance of senescence markers in aging cells [26]. Cellular reactive oxygen species are reduced and, interestingly, mitochondrial integrity is restored. Specifically, catalase-SKL expression reestablishes mitochondrial membrane potential (normally dissipated as cells age [29]) and reduces mitochondrial reactive oxygen species production (normally elevated in senescing cells [26,29]).

The latter results suggest that a redox-sensitive peroxisome–mitochondria interplay is at work in cells. Importantly, this extends evidence of organelle cross-talk and functional cooperation previously summarized by Dr. Michael Schrader and colleagues [30,31]. With the suggestion of such a relationship in mind, it is probably not surprising then, that inactivating catalase with 3-amino-1,2,4-triazole drives mitochondria to a depolarized [16], reactive oxygen species-producing, state [16,32]. Peroxisomal catalase is cytoprotective; its absence, mislocalization, or inactivation is progeric on cells, which begs the question; can the antioxidant enzyme be introduced to cells — and if so, would we not expect a significant effect on age-, or oxidative stress-induced cellular pathologies?

[2] Peroxisome proliferation may also reflect impaired turnover of the organelle. Chaperone-mediated autophagy is compromised with age [27]; whether or not autophagic processes directly responsible for peroxisome turnover are similarly affected is not clear. However, see relevant references included in [3] and [28] regarding links between cell senescence/aging and impaired autophagic pathways.

3.4. Cell penetrating catalase-SKL

Catalase-SKL contains a reengineered peroxisome targeting signal at its carboxy terminus. This enzyme interacts more avidly with the import receptor, Pex5p [26], and is more efficiently imported into peroxisomes [26]. The molecule was developed into a protein therapeutic by adding a cell penetrating peptide near the amino terminus, along with a polyhistidine tag — used for purifying the recombinant enzyme (see Fig. 1 schematic). The following is a brief summary of the demonstrated efficacy of the cell penetrating antioxidant enzyme (hereafter referred to as CAT-SKL) in a number of cell biological, physiological, and pathophysiological contexts.

In a human cell model for psoriasis, CAT-SKL reduces tumor necrosis factor-α-induced reactive oxygen species and downstream inflammatory cytokine production [33]. In primary explants of human skin, a topically applied hydrogel preparation of CAT-SKL reduced ultraviolet light-induced lipid peroxidation by more than 60% as compared to a formulation base alone [34]. The molecule, when formulated with appropriate excipients including skin penetrating agents, enters (mouse) skin and reduces hydrogen peroxide levels [34]. Importantly, repeat insult patch test results indicate that the CAT-SKL hydrogel elicited no "contact sensitization" reactions of any kind when applied over 10 weeks to human subjects [34].

The results in skin may be relevant to radiation dermatitis — a side effect of certain cancer treatments. Collaborative studies conducted at our own institution [35] showed that CAT-SKL inhibited photodynamic therapy-induced apoptosis in murine leukemia cells. In contrast, the catalase inhibitor, 3-amino-1,2,4-triazole, potentiated the response. These studies are important in that they demonstrate a role for hydrogen peroxide in photodynamic therapy's pro-apoptotic effects, and suggest that CAT-SKL might be beneficial, that is, protective, if applied to tissue adjacent to that undergoing a photodynamic therapy-based treatment regimen. Also, the idea that inhibition of antioxidant activity enhances photo- or radiation-killing may have important implications for tumor elimination strategies.

Reactive oxygen species and resultant oxidative stress are thought to be the main drivers of ischemia–reperfusion and hypoxia–reoxygenation injuries in the heart. Our work with a neonatal ventricular myocyte model showed CAT-SKL protected cells against these injurious events [36]. Coupled with our unpublished evidence that the targeted antioxidant reduces the area of necrosis, as a function of the area at risk, in rats exposed to a 30 min ischemic event — the suggestion is that CAT-SKL may represent a potentially powerful new therapeutic modality for the protection of heart tissue from oxidative damage.

In two other as yet to be published lines of research, CAT-SKL reduced the toxic effects of soluble β-amyloid peptides on cultured embryonic rat hippocampal/cortical neurons [34], and sensitized otherwise resistant breast cancer cells to the tyrosine kinase inhibitor, gefitinib [37]. With respect to the former, these studies corroborate work from Dr. Nibaldo Inestrosa and colleagues [38] showing a protective role for peroxisomes and peroxisomal catalase in β-amyloid induced neurodegeneration.

Non-SKL derivatized cell penetrating catalase molecules have also been employed in a number of systems including those designed to

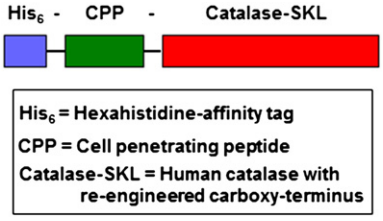

Fig. 1. CAT-SKL construct. See text for additional description.

have the enzyme enter skin [39], to modulate ischemia–reperfusion injuries in the heart [40], and to identify hydrogen peroxide-dependent signaling pathways [41]. Regarding this last point; our unpublished work looking at gene arrays and the effects of CAT-SKL suggest elimination of CAT-SKL-sensitive reactive oxygen species may reintroduce cell cycle checkpoint control in senescing cells. The fact that catalase-SKL delays appearance of senescence markers [26], whereas mislocalized catalase is associated with the senescent state [25], is certainly consistent with these preliminary results.

One large emission from these completed or ongoing studies is a longitudinal analysis, in animals, of the effects of supplementing peroxisomal catalase. This could be accomplished, for example, in a transgenic background with catalase-SKL as the introduced exogenous gene. Catalase-SKL would be the preferred transgene to assure more robust peroxisome trafficking with age [25,26]. An alternative approach could involve regular (intraperitoneal or subcutaneous) administration of the recombinant protein, CAT-SKL. There are advantages and disadvantages of both approaches including the considerable time and expense of the requisite protocols. However, generation of these animals would permit not only a longevity study, but also an evaluation of their disease resistance after appropriate crosses or physiological perturbations. One could reasonably expect such animals to delay onset of age-related degenerative disease and perhaps even live longer than control animals. Of course, this is simply conjecture at this point.

Some final thoughts on catalase. One recurring question is why does catalase possess a weak perosixome targeting signal — a property of the enzyme seen across evolutionary diverse organisms. Is it that a kinetically delayed import process permits proper folding and assembly of constituent protein and heme subunits? Is it, as speculated previously [42], that import of the enzyme is sufficiently robust in young cells/organisms and that the compromised compartmentalization seen in aging occurs after reproductive age and cannot be selected against evolutionarily? Is it that advantages exist for catalase to be partially localized to the cytosol? With respect to the latter, consider that during red blood cell development, precursor cells eliminate intracellular organelles [43]. Perhaps a partial cytosolic localization preserves antioxidant capacities in the mature red blood cell.

Lastly, overexpression of catalase in and of itself is not a panacea. Several studies over the years have shown that enhanced levels of antioxidant enzymes or mimetics may actually sensitize cells to toxic insult — not insulate them. As pointed out recently by Dr. Epstein and colleagues [44], catalase overexpression in β-cells of the mouse pancreas actually sensitizes the animal to diabetes. Their explanation, and one supported by an emerging consensus, is that indiscriminate metabolism of reactive oxygen species in cells may very well be detrimental. Reactive oxygen species in small amounts (~bursts) and in particular locations, represent critical components of signaling cascades and related communication networks. They cannot be indiscriminately metabolized by broad-acting, non-targeted antioxidant strategies.

4. Conclusions and perspectives

Fig. 2 depicts a schematized version of two cells; a young cell at early passage, and an old cell at, or near, replicative senescence. The albeit simplified rendering reveals several important points. First, reactive oxygen species can emanate from peroxisomes and mitochondria — even in young cells. The idea has emerged that these organelles might release a small but continuous stream of the reactive molecules to maintain readiness of the antioxidant response as well as to appropriately regulate cell signaling, cell communication, and network integrating activities. The sum total of these "hormetic" or "preconditioning" pathways may very well be the anti-aging programs reviewed in [14]. However, the perspective of this article has been on what happens when these reactive oxygen species are produced beyond a specific threshold — when they

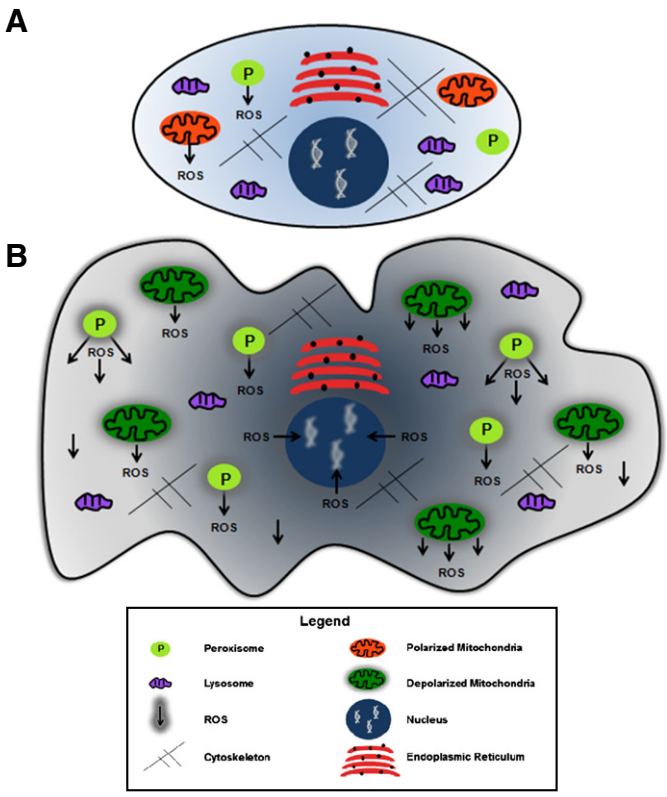

Fig. 2. Schematic representation of cellular senescence and its impact on organelles, reactive oxygen species production, and cell architecture. A. As described in the text, early passage/young cells contain peroxisomes and mitochondria that are fully capable of processing reactive oxygen species produced in situ. B. Late passage/old cells are less able to carry out these processes and amass the reactive metabolites. As a consequence they manifest changes to organelles and the cell itself as illustrated.

begin to amass and damage cell constituents and to initiate more pro-aging programs. As we depict in the figure, peroxisomes and mitochondria release reactive oxygen species — with each organelle affected by the process. Peroxisomes proliferate with age [25,32], as do mitochondria [45]. Peroxisomes are impaired in their ability to import their constituent enzymes, [25,32], and begin to manifest functional deficits. Mitochondrial functionality is also reduced — for example, their ability to maintain a membrane potential is impaired [26,29]. It should be noted that mitochondrial DNA is exquisitely sensitive to oxidative stress and an accumulation of mutations is seen as a major driver of mammalian aging [46].

It is nearly impossible to tease out where reactive oxygen species begin and end in the cell. Is hydrogen peroxide produced first in the peroxisome and then "efficiently" diffuse to mitochondria where it attacks perhaps more delicate components of the electron transport chain? Or does trafficking of the reactive metabolite and its downstream derivatives originate in mitochondria — the cell's "fiery furnace"? Continuing with unanswered questions, only little has been included here about the precise targets of organellar, or otherwise produced, reactive oxygen species. What signaling pathways, communication networks, and pro- or anti-aging programs are actually modulated by these reactive molecules? It has been questioned whether aging represents a sort of end point with respect to oxidative damage to cellular constituents — or is it the culmination of an as yet undefined, development program? What is clear is that cellular reactive oxygen species — and hydrogen peroxide in particular, is as suggested by Drs. Teng Lu and Toren Finkel, a "primary mediator" of in vitro senescence and in vivo aging [47]. Echoing the importance of hydrogen peroxide, Drs. Michael Lisanti, Federica Sotgia and co-authors suggest the molecule, via its ability to "drive accelerated aging", constitutes a major player in the etiology of inflammation and cancer [48].

What has long been ignored when considering the nexus of oxidative stress, aging, and the development of degenerative disease is a role for peroxisomes. Although the extent of this role is yet to be completely defined — it is quite clear that peroxisomes will continue to emerge as critical contributors to these processes.

Conflict of interest

SRT is a cofounder of EXT Life Sciences, Inc., a Michigan-based biotechnology company owned, in part, by Wayne State University. SRT retains an equity interest in the company that is developing CAT-SKL, one of the antioxidants discussed in this article. CRG reports no conflict of interest.

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