Nutraceutical Strategies for Controlling the Secretory Phenotype Associated with Cellular Senescence

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Abstract

The proportion of senescent cells in tissues increases with increasing age. Senescent cells tend to adopt a "senescence-associated secretory phenotype" (SASP) associated with increased secretion of pro-inflammatory cytokines, notably interleukins 6 and 8. There is reason to suspect that a pro-inflammatory impact of the accumulation of senescent cells contributes to the structural and functional deficits of aging, while also contributing to cancer progression. Senescent cells often express interleukin-1a (IL-1a), and there is evidence that IL-1a is an obligate driver of SASP in senescent fibroblasts. Interleukin-1 is also a key mediator of chondrocyte inflammation and cartilage matrix catabolism in osteoarthritis; a number of nutraceuticals with potential for antagonizing IL-1 signaling in chondrocytes have been defined. It is tempting to speculate that these same nutraceuticals may likewise block SASP induction in senescent cells by opposing IL-1 activity. Phycocyanobilin, phase 2 inducer phytochemicals, AMPK activators such as berberine, and glucosamine may merit evaluation in this regard. Curiously, regular glucosamine use has been linked to reduced total mortality and cancer risk in recent epidemiology; could this reflect suppression of SASP?

Cellular Senescence - A Likely Mediator of the Aging Process

Cells threatened by significant DNA damage, excessive mitotic stimulation (often stemming from activation of oncogenes), or severe energy deficit, often respond by undergoing a transition to "cellular senescence".[1] Senescent cells remain viable, but are characterized by an irreversible loss of capacity to divide; this loss of mitotic capacity is typically associated with, and driven by, increased activity of p53 and/or p16INK4a.[2] Senescence prevents a cell under severe stress from giving rise to cancer, and represents an alternative to apoptosis or necrosis in this regard. Senescent cells are prone to being scavenged by natural killer cells, a phenomenon which keeps the total population of senescent cells under control. Nonetheless, the proportion of senescent cells within the body's tissues tends to increase with aging, giving rise to the hypothesis that cellular senescence may promote some of the phenotypes associated with aging.[3]

Senescent cells tend to adopt a "senescence-associated secretory phenotype" (SASP) associated with increased production and secretion of certain inflammatory cytokines, most notably interleukins 6 and 8.[4] Constitutive activation of transcription factors NF-kappaB and C/EBPβ appears to be a key mediator of SASP.[5] It is suspected that the pro-inflammatory impact of senescent cells within the tissues of aging individuals contributes to the structural and functional decrements that characterize aging.[3] Arguably, cellular senescence may contribute significantly to the age-related increase in serum IL-6 which Ershler and colleagues have proposed to be a key driver of the aging process.[6-8] Moreover, incubation of initiated non-senescent cells with senescent cells, or culture medium derived from senescent cells, has been found to promote cancer progression.[9] IL-6 has the potential to trigger stem cell behavior and epithelial-mesenchymal transition in transformed cells, rendering cancers more aggressive and difficult to treat.[10-12]

Hence, although senescence prevents an individual cell from giving rise to cancer, the pro-inflammatory cytokines produced by that senescent cells may increase the probability that neighboring non-senescent cells give rise to an aggressive cancer.

BubR1-insufficient mice, in whom progressive DNA damage gives rise to a progeroid syndrome, are highly prone to cellular senescence.[13] In adipose tissue, skeletal muscle, and the eye, the senescent cells of BubR1-insufficient mice strongly express p16INK4a. Baker and colleagues, employing a technique which selectively kills p16INK4a-expressing cells in genetically modified strains of BubR1-insufficient mice, have shown that elimination of these senescent cells strongly protects the mice from the sarcopenia (associated with lordokyphosis), atrophy of adipose tissue, and cataracts typically seen in aging BubR1-insufficient mice.[14] This study provides direct proof that the SASP of senescent cells has the potential to contribute importantly to the structural and functional deficits of aging. The extent to which this phenomenon plays a role in the aging of genetically "normal" animals requires further clarification.

Interleukin-1a Induces the Senescence-Associated Secretory Phenotype

How does SASP arise in senescent cells? Cellular senescence is associated with increased production of IL-1α.[15, 16] Campisi and colleagues have provided compelling evidence that, at least in senescent fibroblasts, increased expression of cell-bound interleukin-1α is an obligate mediator of SASP.[17] Hence, blockade of IL-1α or its receptor suppressed activation of NF-kappaB and C/EBPβ and largely prevented induction of SASP in fibroblasts subjected to a number of assaults which trigger senescence. Although it is not yet clear whether IL-1α drives SASP in other types of senescent cells, the fact that fibroblasts are key structural components of a high proportion of tissues suggests that IL-1α overactivity may be a key mediator of the aging decrements associated with SASP.

Nutraceuticals Useful for Cartilage Preservation May Inhibit SASP via IL-1 Antagonism

Curiously, IL-1 activity appears to play a key role in the cartilage loss associated with osteoarthritis.[18] IL-1, produced by inflamed synovial cells or in an autocrine manner by chondrocytes themselves, triggers an inflammatory state in chondrocytes, characterized by NF-kappaB overactivation, that exerts a catabolic effect on cartilage matrix. A recent essay has posited that several categories of nutraceuticals have the potential to intervene in IL-1 signaling in chondrocytes, thereby preventing loss of cartilage matrix.[19] These nutraceuticals include phycocyanobilin – which has the potential to prevent the activation of chondrocyte NADPH oxidase, an aspect of IL-1 signaling that aids NF-kappaB activation;[20-23] phytochemical phase 2 inducers, which boost cellular expression of glutathione and of a range of antioxidant enzymes, including heme oxygenase-1 (HO-1);[24-28] AMPK activators such as berberine, which may antagonize NF-kappaB activation via several complementary mechanisms;[29] and glucosamine - which somehow suppresses the pro-inflammatory impact of IL-1 on chondrocytes in cell culture, [30-35] exerts chondroprotective effects in animal models of osteoarthritis,[36-38] and – despite controversy regarding its utility for pain control in clinical osteoarthritis[39, 40] - has been found to preserve cartilage in patients with osteoarthritis of the knee.[41, 42] It is intriguing to speculate that such measures might likewise have potential for blocking or reversing SASP in senescent fibroblasts, and possibly other types of senescent cells in which IL-1 drives SASP.

The antioxidant impact of phycocyanobilin and of phase 2 inducers may have the potential, not only to inhibit induction of SASP, but also to block induction of senescence in cells at risk for oxidatively-

mediated DNA damage.[43] Indeed, phycocyanobilin appears to mimic the physiological antioxidant activity of free bilirubin (a key product of HO-1), and it is intriguing that prospective epidemiological studies have linked elevated baseline serum bilirubin levels with reduced incidence of, or mortality from, cancer.[44, 45] Arguably, this phenomenon might reflect both protection from initiating DNA damage, and suppression of SASP. Activation of AMPK likewise has been reported to decrease cellular markers for DNA damage,[46] and may have great potential for cancer prevention – as well as amplification of healthspan.[47-51] However, strong AMPK activity, via an activating phosphorylation of p53, has been found to promote cellular senescence and p16INK4a expression under certain circumstances.[52-55] Nonetheless, expression of p16INK4a, while it can evoke cellular senescence, is not in itself sufficient to induce SASP.[56] Hence, nutraceutical AMPK activators such as berberine,[57, 58] independent of their impact on cellular senescence per se, may indeed have potential for control of SASP. Moreover, there is evidence that AMPK can interfere with IL-6 signaling, at least in hepatocytes. [59]

Glucosamine may be of particular interest in this regard, in light to several recent prospective epidemiological studies which unexpectedly have observed that regular users of this nutraceutical are at decreased risk for total mortality and for cancers of the lung or colon.[24, 60, 61] Although most of the cell culture studies demonstrating that glucosamine can antagonize IL-1 signaling have employed supraclinical concentrations of this agent, it is notable that oral glucosamine has been reported to prevent increases in serum IL-6 in a rabbit model of atherosclerosis associated with inflammatory arthritis.[62] Hence, it is not inconceivable that oral glucosamine – which has shown not only chondroprotective, but also anti-inflammatory effects in rodent models[63, 64] – has the potential to intervene in IL-1α-driven SASP, and that this helps to rationalize the favorable impact of glucosamine usage observed in epidemiology. This intervention seems likely to reflect O-GlcNAc modification of key signaling intermediates – the mechanism whereby glucosamine inhibits TNF-α signaling in endothelial and vascular smooth muscle cells.[65, 66] Indeed, in TNF-α-treated smooth muscle cells, O-GlcNAc modification of the p65 subunit of NF-kappaB has been found to block an activating phosphorylation of Ser536 required for optimal transcriptional activity.

Rather than expecting any one of these agents to achieve a definitive effect, it might make better sense to explore combinatorial strategies. For example, phycocyanobilin and phase 2 inducers have the potential to block oxidative up-regulation of IkappaB kinase activation; berberine, via Sirt1 activation, may remove an activating acetyl group from p65;[67-69] and glucosamine may inhibit an activating phosphorylation of p65 on Ser536. Even if tolerable and feasible intakes of these agents achieve these effects to only a limited extent, their combined impact on the transcriptional activity of NF-kappaB might prove to be clinically important. Indeed, this strategy might prove to be useful, not just with respect to SASP, but the broad range of disorders in which NF-kappaB-driven inflammation plays a prominent mediating role. (In therapeutic circumstances, one could consider adding the natural agent salicylic acid - best administered as its dimer salsalate - which directly inhibits IKK-β.[70, 71] It is not as practical for use in primary prevention, as effective doses induce reversible auditory side effects in a significant minority of subjects.[72])

Whether or not these specific suggestions prove to have practical clinical utility for suppressing SASP, the goal of defining practical nutraceutical strategies for controlling SASP is worthy of pursuit – particularly if future studies demonstrate that SASP has an important impact on human healthspan.

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