Intervention of aging and its effects on cellular health

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ABSTRACT

Aging is associated with a majority of chronic diseases and conditions. But in itself, aging has not been considered pathological. By taking a more systems-level approach, competing notions around aging and chronic disease can be attributed to a common underlying cellular mechanism known as cellular senescence, a permanent state of cell cycle arrest. By excreting pro-inflammatory signaling molecules, senescent cells influence the local cellular environment and induce "bystander senescence" in neighboring cells. Characterized as senescence-associated secretory phenotype (SASP), this can be seen in many diseased tissues having characteristics associated with cell aging, such as DNA damage, glycation, telomere loss, and oxidative stress. Research shows that likely therapeutic candidates to reduce the effect of senescence involve epigenetic modulation of the cellular environment, in particular with compounds that can influence activity within pathways known to be associated with cellular senescence and SASP. Phytonutrient interventions that address the whole system of cellular health are likely to have the most impactful results on the effects of aging due to cellular senescence.

Competing notions around aging result in "research silos"

Aging places a significant burden on individuals, families, and societies, especially as the demographics of the world's population change. It is also associated with a majority of chronic and debilitating diseases and conditions.[1-3] But, aging in itself has not been considered pathological. Rather, it has been characterized by competing theories[4,5] and divided into a variety of discrete processes.[6] These competing, and sometimes mutually exclusive theories and processes are driven in part by historical accident, meaning the underlying research is often quite narrow in scope. The iteration of that narrow scope over time has produced a significant body of research that is fragmented and that has often produced areas of clinical practice that are functionally siloed, focused on one or another theory or aspect of aging. By taking a more systems-level approach, the competing notions around aging and chronic disease can be recast as "symptoms" all related to a common underlying cellular mechanism.[7,8] This concept of cell health arises from the recent and developing understanding that aging and its associated diseases and impairments are potentially driven by a common mechanism. That mechanism, known as cellular senescence, may be amenable to intervention.

Aging is driven by cellular senescence and SASP

First recognized in cell cultures, senescent cells stop dividing but do not undergo apoptosis. As described by Kirkwood, this is an ongoing process that contributes to aging and, more importantly, the diseases of aging (Figure 1).

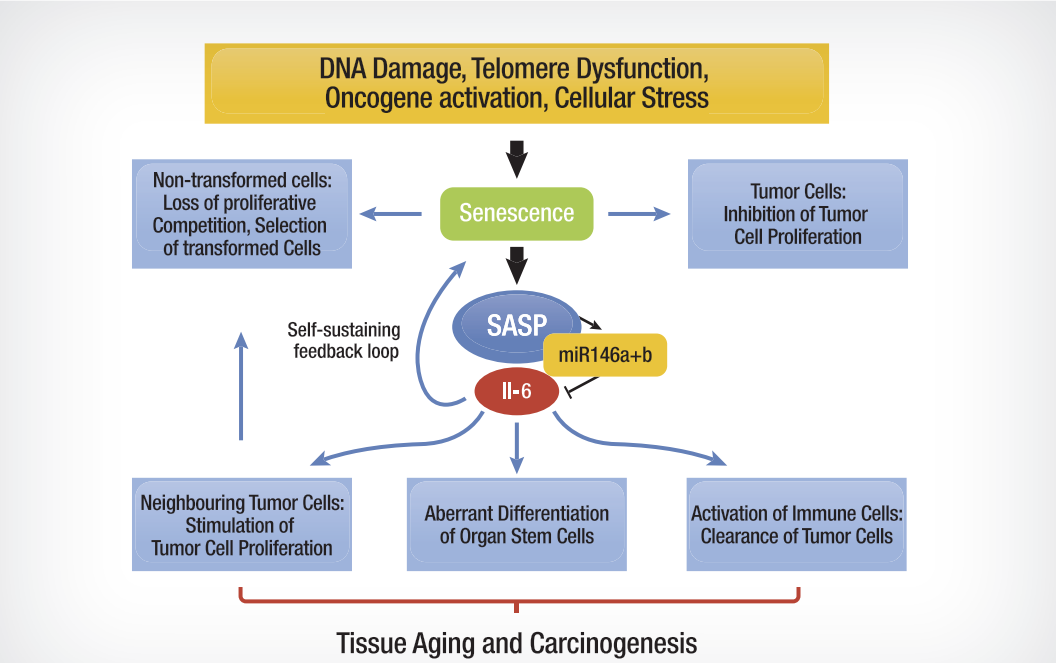

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Figure 1. Senescent cells that fail to undergo apoptosis contribute to aging.[9]

Senescent cells begin to excrete signaling molecules that are pro-inflammatory, so begin to influence the local cellular environment.[8] That influence can induce "bystander senescence" in neighboring cells, essentially spreading senescence locally.[10] This damaging epigenetic profile is characterized as the senescence-associated secretory phenotype (SASP) (Figure 2).

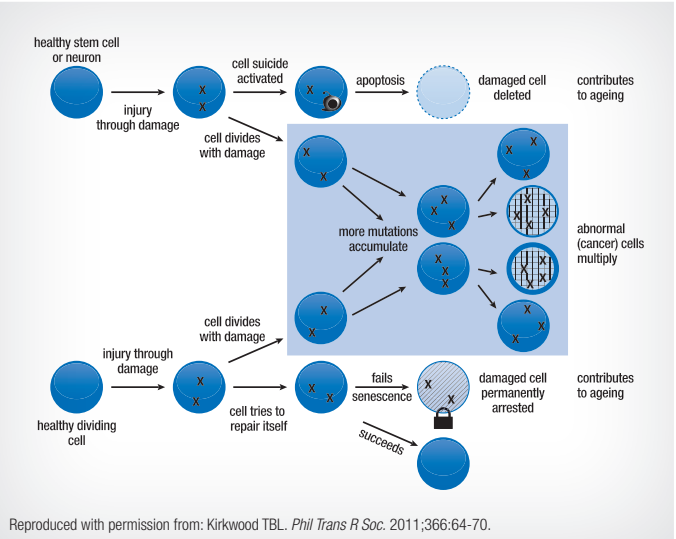

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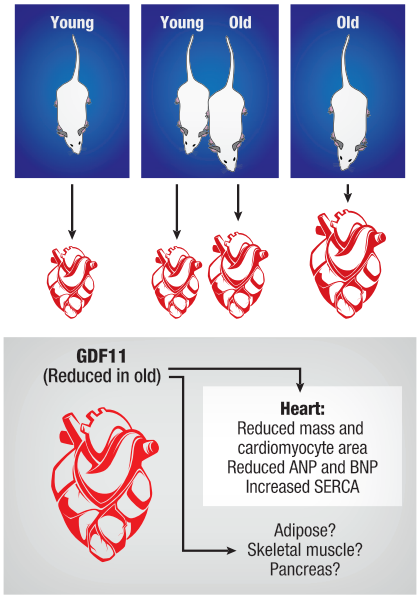
Figure 2. Influence of bystander senescence.[8]

The induction of this pro-inflammatory cellular environment that can spread to other cells can be seen in many diseased tissues and has characteristics associated with cell aging, such as DNA damage, glycation, telomere loss, and oxidative stress. Published literature is available describing the mechanism producing cellular senescence and the consequences of that process.[11-14] These senescent cells, or "quiet little traitors" as they've been called, are likely the common pathway to many of age-related diseases and conditions.[15-20]

The search for potential treatments

Efforts are mounting to further define the role of SASP and cellular senescence in a variety of diseases and age-related conditions as well as search for potential treatments. Strikingly, in research first conducted in the 1860s and resurrected in the recent past, there are methods to arrest and even reverse senescence in animals.[21, 22]

Heterochronic parabiosis is a technique in which the circulatory systems of old and young animals are surgically joined, which has been shown to reverse the effects of aging, such as cardiac hypertrophy (Figure3).[23, 24] These experiments and others have demonstrated that there are paracrine factors that can signal bi-directionally, both reversing aging and cellular senescence in older animals, while inducing age-related symptoms in younger animals.[25-28] The reversal of senescence has also been seen to restore cell function even in aged progenitor cells.[29-32]



Adapted with permission from Leinwand LA, Harrison BC. *Cell.* 2013;153(4): 743-745.

Figure 3. Heterochronic parabiosis can reverse the effects of aging.[24]

These data support the idea that the aging cellular environment is amenable to epigenetic influence and that the processes associated with senescence can be modified. In particular, researchers were able to identify one paracrine factor that, when used by itself outside of direct parabiosis, significantly reversed senescence-associated disease in a cardiac model.[25] This research is centered on understanding which paracrine factors, especially mRNA-containing exosomes, are likely implicated in the improvement of cell senescence in vivo,[33-36] which may lead to the eventual treatment of aging epigenetically.[38-40]

Although these treatments remain many years out in the future, it is clear that epigenetic modulation of the cellular environment, in particular with compounds that can influence activity within pathways known to be associated with cellular senescence and SASP, are likely therapeutic candidates to reduce the effects of senescence—aging in fact—on the higher levels of physiological organization, such as tissues, organs, systems, and individual morbidity and mortality.[41-43]

Intervention of aging with phytonutrients

As described above, cellular senescence is at least partially driven by a number of factors, including DNA damage, free radicals, insulin resistance, and telomere attrition. Developing SASP-targeted treatments to counteract the effects of senescence amount to "treating" aging which, until recently, was considered an arcane idea.[44] But, with the increasing evidence that aging and associated diseases are all driven by SASP, getting at the common core rather than the individualized diseases will likely produce more rapid and useful outcomes and substantially reduce costs.[45] Likewise, simply singling out one of the putative drivers of senescence does not address the overall problem, which is fundamentally an issue within a complex, nonlinear system.[46,47]

One area of intervention includes the use of natural botanicals, phytonutrients, and other naturally occurring compounds to improve the cellular environment and cellular senescence through epigenetic routes,[48] including phytonutrients such as resveratrol, curcumin, and others. In general, these approaches are still hobbled by the fractured approaches that have arisen over time, so particular ingredients are employed to affect particular areas, like resveratrol for circadian control[49] or insulin control,[50] Astragalus for telomere length,[51] and ginseng for its effects on TNF-α.[52] While potentially effective in a specific regard, the aging cellular environment is a system of processes so a single process or intervention aimed at a single area is unlikely to produce a significant change in cellular senescence and more importantly, in the associated pathological cellular milieu.

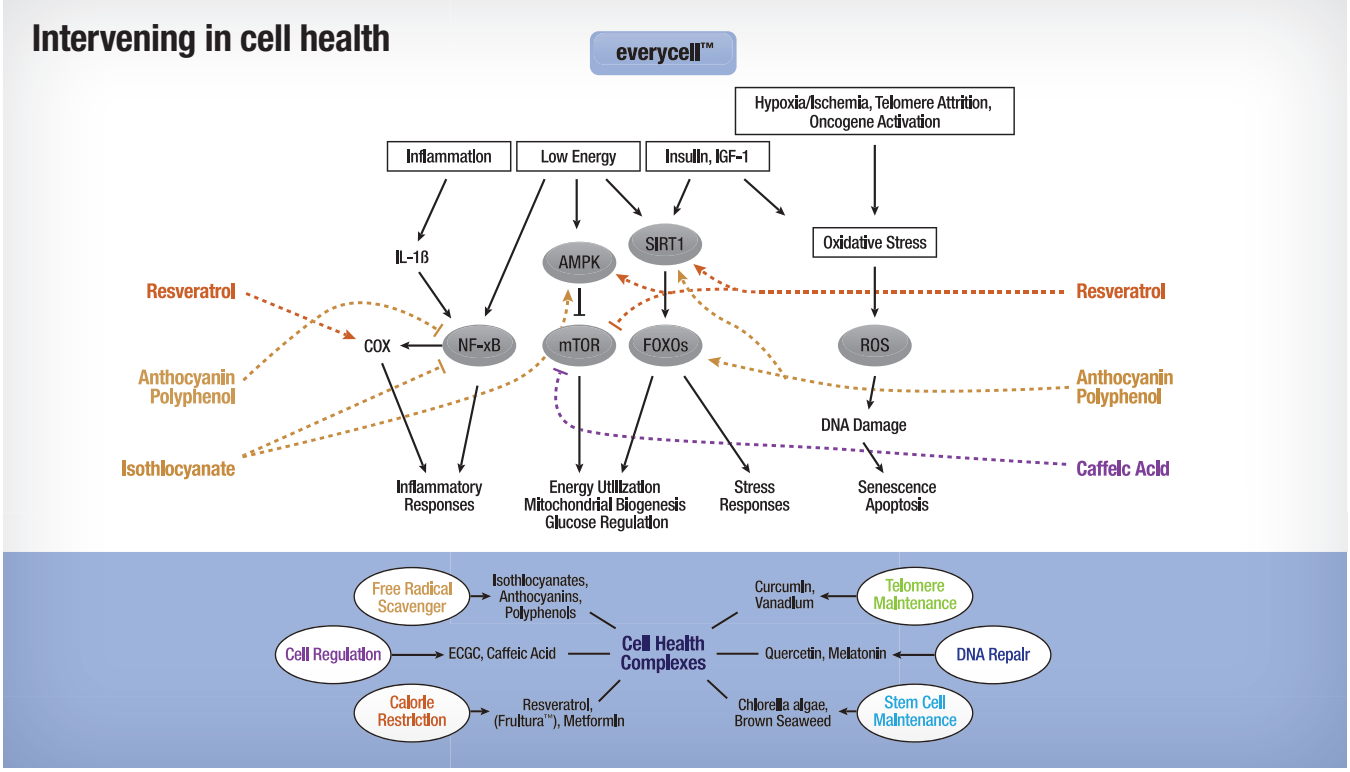


Figure 4. Significant reductions in inflammatory cytokines are seen with initial formulation of healthycell *plus*.

Other investigators, recognizing this as a systems-based issue, have developed multifaceted approaches to specific areas of clinical concern.[53, 54] Although directed at clinical disorders (cancer and neurological), they evaluate the potential effects of a suite of phytonutrients. Likewise, in stem cell activity, multi-ingredient phytonutrient compounds are seen to produce significant improvements.[55, 56]

healthycell™ *plus* may help reduce inflammatory cytokines

The current professional formulation from CellHealth™ Institute, healthycell *plus*, is designed to provide users with the best possible, scientifically supported modulator of the cellular environment. healthycell *plus* is composed of multiple phytonutrients, all selected for their synergistic effects within the domains associated with the generation of cellular senescence and SASP. Supported by a randomized controlled trial on an initial formulation that showed reductions in inflammatory cytokines, healthycell *plus* and related formulations have been in use for over a decade, with no known adverse effects within a large group of long-term users.[56]

Phytonutrients are grouped in specific domains critical for improving the cellular environment, maintaining overall cell health, and improving stem cell activity. These domains: free radical scavenging, cell regulation, telomere maintenance, DNA repair, stem cell maintenance, and calorie restriction (insulin resistance) encompass the domains that both drive, and are driven by, cellular senescence. Ongoing clinical research is assessing the objective effects of healthycell *plus* in these domains while continual feedback from users has demonstrated improved sleep, enhanced energy, and improved mental focus.[57]

Conclusion

Cellular health is emerging as the core determinant of aging and the principle driver of age-related diseases. Research supports this idea, as well as the notion that modulating the epigenetic environment will produce significant improvements in the cellular environment, potentially reaching clinical relevance. While pharmaceutical advances are many years off, phytonutrient interventions are available and those that address the whole system of cellular health are likely to have the most impactful results. healthycell *plus* is one of the few existing products designed to address cell health, modulate cellular senescence, and improve the cellular environment, ultimately affecting the core processes in healthy aging. Improving the cellular environment may reduce long-term morbidity and mortality, and result in a longer, higher quality of life, exactly what we all strive to provide for our patients.

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