dramatically enhanced the adaptive immune response, with higher recruitment of naïve MVA-specific CD8+ T cells to the lymph, leading to greater numbers of virus-specific effectors and a broadened T cell repertoire.

Although other groups have reported the importance of the inflammasome in SCS macrophages after viral infection[3,9], the visualization by Sagoo *et al.*[7] of inflammasome activation *in vivo* as a spatially defined wave extends our understanding of SCS macrophages in viral infections. SCS macrophages have been dubbed immune 'flypaper' on the basis of their efficient acquisition of lymph-borne particulates[1]. The programmed pyroptosis of macrophages to disseminate ASC specks, however, makes them more similar to a network of land mines positioned at the entrance of lymph nodes, exploding upon infection rather than acting as a simple filter for incoming pathogens. It will be important to determine whether this occurs in other cells that also become infected, such as dendritic cells (DCs)[10]. As DCs (and not macrophages) prime T cell responses in the node, DC death could be costly to the host, although it may be necessary to prevent intracellular pathogen replication. It will be of great interest to examine both the contribution of inflammasome-driven pyroptosis to the control of viruses that replicate and spread in lymph nodes, and the consequences of programmed macrophage deletion.

The inflammatory amplification of adaptive immunity also raises possibilities for rational vaccine design. Strategies to deliberately trigger nodal macrophage inflammasomes could be used as an adjuvant for many types of vaccines, including simple protein-based vaccines. As a testament to the importance of inflammasome activation for controlling virus infection, MVA (and other large DNA viruses) encode proteins that block inflammasome activation. Indeed, the genomic deletion of just one of these immunomodulatory proteins dramatically reduces virulence in replicating poxviruses, and it enhances T cell responses in an MVA-based vaccine candidate[11,12]. Shedding light on inflammasomes *in vivo* could further enhance our ability to manipulate activation at appropriate times during the immune response.

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Depleting senescent cells to combat aging

Hartmut Geiger

A new study in mice suggests that pharmacologically targeting the apoptosis proteins BCL-2 and BCL-xL can clear senescent cells from bone marrow and ameliorate stem cell function during aging, bringing us a step closer to preventing senescence-associated tissue attrition in the clinic.

Senescent cells, now identifiable by a validated set of independent markers, accumulate in tissues during aging or upon tissue damage induced by stimuli such as irradiation[1]. Multiple distinct roles for senescent cells in tissues have been suggested. However, it is now commonly accepted that senescent cells contribute to tissue attrition and to aging-associated initiation of cancer, in part via the factors they secrete, collectively known as the senescence-associated secretory phenotype (SASP). Senescent cells, both *in vivo* and *in vitro*, often express p16(Ink4a), a cyclin-dependent kinase inhibitor that is also known as CDKN2A. Expression of p16(Ink4a) normally renders the growth arrest associated with senescence irreversible[2]. Previous studies have suggested that inducible deletion of cells expressing p16 (Ink4a) at a young age in a genetic model of premature aging delayed the onset of premature-aging initiated diseases in adipose tissue, skeletal muscle and eye tissue[3]. In the same study, late-in-life deletion of cells expressing p16(Ink4a) at least delayed the progression of these diseases. Accordingly, the removal of senescent cells may prevent or delay tissue dysfunction and extend healthspan upon 'normal aging'. However, pharmacological approaches to targeting senescent cells have not been very successful so far, and thus senolytic drugs (small-molecule compounds that selectively remove senescent cells) have only recently been seen as a viable method of delaying senescence. By comparing the transcriptome of senescent and non-senescent cells, two cell type–specific senolytic drugs were recently discovered[4] that improved tissue function in response to cellular senescence induced *in vivo* by ionizing irradiation. Whether the drugs directly acted on senescent cells *in vivo* was not determined. An article in this issue of *Nature Medicine* now demonstrates that pharmacological depletion of senescent cells *in vivo* indeed results in a functional rejuvenation of stem cells in naturally aged mice[5].

Chang *et al.*[5] first tested a panel of small-molecule compounds known to target pathways that were predicted to be important for the maintenance of senescence *in vitro*. They titrated these compounds *in vitro* into cells after exposing them to ionizing irradiation. This revealed that the small-molecule compound ABT263, which is a specific inhibitor of the apoptosis genes *BCL2* and *BCL2L1* (encoding BCL-2 and BCL-xL, respectively), selectively induced apoptosis of senescent cells in culture in a cell type– and species-independent (mouse as well as human).

The authors then carried out experiments in a mouse model known as p16-3MR-these mice carry a trimodal reporter protein (called 3MR) under control of the p16INK4a (p16) promoter[6], and they can be used to identify, track (via bioluminescence) and selectively kill p16-positive senescent cells *in vivo*[5]. When ATB-263 was given to p16-3MR mice, ABT263 effectively depleted senescent cells in bone marrow, lung and muscle tissue, both in naturally aged animals as well as in those treated with a minimal dose of ionizing irradiation, which induces cellular senescence and

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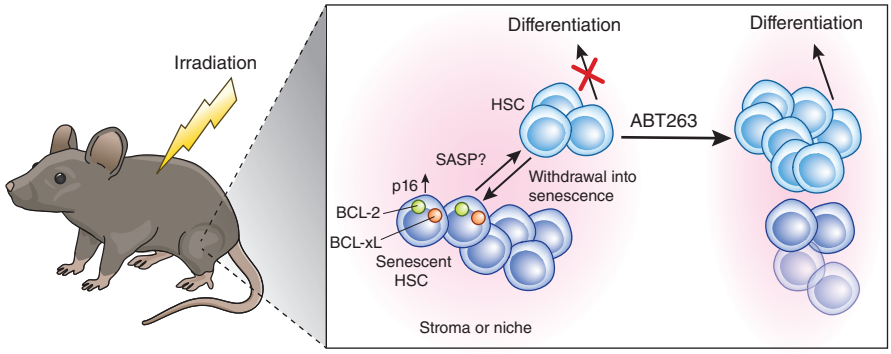

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Figure 1 Senescent cells in bone marrow are killed by ABT263. Senescent cells (shown in dark blue) in the bone marrow are formed from hematopoietic stem cells (HSCs; shown in light blue) as they age, and they may also be induced by radiation in mouse models. They are thought to contribute to aging (and, in turn, induce further senescent cells) in part by the SASP. Chang *et al.*[5] find that ABT263 treatment depletes senescent cells expressing p16 from aged as well as irradiated mice, which then allows the remaining aged or prematurely aged HSCs to functionally rejuvenate, resulting in differentiation. ABT263 inhibits BCL-2 and BCL-xL.

premature aging of the hematopoietic system *in vivo*[7]. As a consequence, ABT263 was able to revert premature aging of hematopoietic stem cells and muscle stem cells (**Fig. 1**). By several experimental approaches, the authors were able to confirm clearance of senescent cells by ABT263; they used bioluminescence in live animals to track removal of p16-positive cells, and they confirmed a reduction in expression of p16 and of gene products involved in SASP (such as interleukin-6) by quantitative PCR[5]. Mouse strains such as p16-3MR, which allow direct tracking of senescent cells *in vivo*, might become the gold standard for the identification of novel senolytic drugs.

The authors' data demonstrate that ABT263 is a senolytic drug that acts in a highly specific manner on many different tissues to target senescent cells both in culture and *in vivo*[5]. These findings bring us a significant step closer to targeting cell senescence in the clinic. Furthermore, these data also support an exciting concept that was recently developed, which is that aging of somatic stem cells is reversible. Hematopoietic stem cell rejuvenation has now been achieved by various (probably) distinct mechanistic approaches, such as by removing senescent cells either in the stroma or among the stem cell pool itself, or by pharmacologically or nutritionally targeting distinct regulatory signaling pathways intrinsic to stem cells[8–10]. Preventing senescence might thus also commence healthier aging.

There are a number of crucial issues that need to be further addressed before we can proceed to developing senolytic drugs for clinical use. For example, a possible initial clinical application might be to target tissue damage initiated by senescent cells that arise in response to, for example, cancer-related chemotherapy. Whether senolytic approaches work directly on the target cells or whether changes in the SASP are the underlying mechanism resulting in tissue rejuvenation should be further investigated to further improve efficacy of the treatment and to reduce probable off-target effects. In addition, there is ample evidence in the literature that cellular senescence serves as a tumor-suppressor mechanism[11]. Although so far the few mice treated with ABT263 in this study did not develop leukemia or other types of cancer, as might be expected from expanding hematopoietic stem cells, additional experiments need to be carried out with larger numbers of mice to better quantify this risk. Finally, ABT-263 treatment has previously been shown to cause toxicities such as thrombocytopenia in the clinic, thus rendering direct clinical use of ABT263 as a senolytic drug, especially in the context of aging, highly unlikely[12]. It will be interesting to see whether we find new drugs that act simultaneously against BCl-2 and BCL-xL that present with less toxicity, or whether targeting these molecules is always linked to thrombocytopenia. These are thus exciting times for targeting senescence with senolytic drugs.

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Tau toxicity feeds forward in frontotemporal dementia

David C Rubinsztein

A new study shows that aggregated forms of tau that cause frontotemporal dementia impair proteasome activity. Furthermore, proteasome inhibition can be alleviated by a small molecule that leads to proteasome phosphorylation and activation, thereby reducing tau accumulation.

Tau is a microtubule-associated protein that accumulates in intracytoplasmic aggregates in Alzheimer's disease and in various frontotemporal dementias called tauopathies. Some of these tauopathies are caused by autosomal-dominant tau mutations, which suggests that tau aggregation is sufficient to mediate neuropathology[1]. The aggregation of proteins such as tau is determined in part by their intracellular concentrations, which are influenced in turn by their degradation rates. Tau can be degraded by both lysosomal processes, such as autophagy, and the ubiquitin-proteasome system[2]. In this issue of *Nature Medicine*, a study[3] describes an important mechanism of tau toxicity in which aggregates impair proteasome activity, which leads to more tau accumulation and oligomerization, probable further impairment of the

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