Editorial

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Future Medicinal Chemistry

The emerging field of senotherapeutic drugs

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"the discovery that small molecules can act as selective eliminators of senescent cells (senolytics) or as inhibitors of SASP (senomorphics) opened the way to an exciting new field of research aiming at the development of senotherapeutics; drugs that can interfere with and delay the aging process and, consequently, exert a therapeutic effect on age-related disorders"

First draft submitted: 11 June 2018; Accepted for publication: 8 August 2018; Published online: 16 September 2018

Keywords: BCL-2 • cellular senescence • dasatinib • drug repurposing • metformin • natural products • NF-κB • PI3K/Akt • quercetin • senescence-associated secretory phenotype • senolytics • senomorphics • target-based drug discovery

The cellular phenomenon of senescence is nowadays widely recognized as one of the hallmarks of the aging process [1,2]. The fundamental characteristic of senescent cells is an irreversible cell cycle arrest. Nonetheless, this proliferative incompetency is not accompanied by apoptosis but by a markedly increased metabolic activity and a highly specific and complex secretory phenotype involving pro-inflammatory cytokines, chemokines, tissue-damaging proteases and growth factors collectively referred to as the senescence-associated secretory phenotype (SASP). Senescence can be induced either as a result of telomere shortening (replicative senescence) or as a response to cellular stressors such as UV radiation, increased levels of ROS species, DNA damage and tumorigenic signals including oncogene expression (cellular senescence) [3]. Due to the underlying biological complexity, identification of senescence is not trivial and to this end, several biomarkers have been utilized. Among them, the most robust are elevated expression levels of the endogenous CDK inhibitors $p16^{INK4a}$ and $p21^{CIP1}$, increased activity of the lysosomal enzyme senescence-associated β-galactosidase (SA-β-gal) and accumulation of lipofuscin, a nondegradable by-product of aging [4].

Senescence was originally understood as a defensive mechanism against proliferation of potentially transformed cells. Subsequently, a number of additional beneficial functions of equal importance such as tissue repair, wound healing and embryonic development came into light [2]. However, it is now well accepted that cellular senescence is causally associated with the onset and progression of a multitude of serious age-related pathologies. Chronic accumulation of senescent cells has been related with neurodegenerative and metabolic diseases, cancer, cardiovascular abnormalities, disorders of the liver, bone and skin, as well as infectious diseases [5]. Indeed, even though senescent cells are normally cleared by the immune system, identification of significant populations of such cells at pathological sites is a consistent finding. The deleterious effects of senescent cells are propagated to the neighboring tissue environment through a multitude of mechanisms that are principally triggered by signals associated with the SASP secretome and include homeostatic aberrations, persistent inflammatory responses, deterioration of the stem cell niche, angiogenesis, induction of epithelial-to-mesenchymal transition, fibrosis and establishment of conditions that promote survival and proliferation of cancer cells [2].

In the last 10 years, ground-breaking studies have provided proof of concept that either relieving the burden of senescent cells or suppressing SASP can have a beneficial impact to age-related abnormalities, thus ameliorating the health state of an organism and subsequently increasing life span [6]. To this direction, the discovery that small molecules can act as selective eliminators of senescent cells (senolytics) or as inhibitors of SASP (senomorphics) opened the way to an exciting new field of research aiming at the development of senotherapeutics; drugs that can interfere with and delay the aging process and, consequently, exert a therapeutic effect on age-related disorders [6].

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Of seminal importance for establishing senotherapeutics as a highly promising field in drug discovery are studies performed in Mayo Clinic by the Kirkland group [7–10]. The first molecules to be identified as senolytics in 2015 were dasatinib, a kinase inhibitor in clinical use and quercetin, a rather common flavonoid [7]. Both were discovered by following a rational approach involving target validation, genetically modified animals, transcriptomic analysis and bioinformatics. The molecular targets associated with the observed senolytic effects were Eph receptor tyrosine kinases and PI3K/AKT pathway modules, respectively. This discovery prompted further investigations and navitoclax (ABT-263) was the third senolytic to be identified [11]. Navitoclax is a protein–protein interaction inhibitor targeting the BCL-2 family of apoptotic proteins and, in this case, the effect was specifically attributed to inhibition of BCL-XL and BCL-W. The finding that BCL-2 inhibitors can act as senolytics assisted the additional identification of analogs A1331852, A1155463 and ABT-737, investigational drugs that inhibit BCL-2 family members, as senolytics [8]. In the same context, the potential of the flavonol fisetin and the alkaloid piperlongumine against senescent cells was subsequently established [8,12]. The mechanism of action for fisetin is likely related with PI3K/AKT/mTOR and NF-κB pathway modules as in the case of quercetin. On the other hand, the corresponding activity of piperlongumine was shown to be independent of ROS production, the suggested mechanism of action for apoptotic effects demonstrated by this natural product in cancer cells, but rather related with the NF-κB pathway, thus indicating overlapping mechanisms in the senolytic properties of both alkaloids and flavonoids [12].

Two key observations were derived by these pioneering studies. The first was that senescent cells are heavily dependent on pro-survival and antiapoptotic pathways and as a result, targeting modules of these signaling cascades can enable selective elimination of aged cells and offer the desired specificity over healthy cells. The second observation was that the senolytic effect appears to be strongly cell-type dependent, thus posing obstacles in developing experimental settings for evaluating senotherapeutics *in vitro*. These early research efforts provided a firm rationale for evaluating the activity of drug-like molecules against senescence and an increasing number of studies emerged in the following years, including several reports based on *in vivo* experiments. Natural products continued to emerge as senolytics but interesting senomorphic activities were also recorded for compounds belonging to similar scaffolds. Flavonoids, such as kaempferol and apigenin were attributed with substantial capacities to suppress SASP, possibly by interfering with components of the NF-κB pathway [13]. On the other hand, resveratrol and several synthetic analogs were evaluated as inhibitors of the senescence phenotype and their activity was associated with restoration in the expression of RNA splicing factors, which was notably independent from activation of SIRT1, the enzyme considered as the main mediator of lifespan extension properties attributed to this natural stilbenoid [14]. Polyketides comprise a different class of natural products characterized by a promising senotherapeutic potential. Geldanamycin, tanespimycin and rapamycin were studied in different settings and, regardless of their fair structural similarity, their activities against senescent cells were found to be mediated by markedly different pathways [9,15]. Concerning the two first macrolides, the main mechanism of senolytic action was inhibition of HSP90 coupled with a consequent PI3K/Akt downregulation [9]. Conversely, rapamycin did not act as a senolytic but rather as a potent SASP suppressor through a complex mechanism including inhibition of its main target, mTOR kinase, accompanied by involvement of both Nrf2-dependent and independent modules [15].

However, at present the most interesting aspect in the field of senotherapeutics is drug repurposing. Apart from dasatinib and rapamycin, in the last 3 years at least six clinically used drugs have been attributed with potent activity either against survival of senescent cells or SASP. The discovery that the JAK/STAT inhibitor ruxolitinib could alleviate SASP-related dysfunctions and frailty has indicated reduction of activin-A levels as a possible mechanism of action and JAK1/2 kinases as potential targets for senotherapeutic interventions [10]. On the other hand, cotreatment with the HDAC inhibitor panobinostat and taxol was shown to greatly improve therapeutic results of the latter, with recorded synergies mainly attributed to the senolytic potential of panobinostat [16]. Glucocorticoids are a different class of widely used drugs recently characterized by senotherapeutic activity, although rather inconclusively. Whereas cortisol and corticosterone demonstrated a strong capacity to inhibit SASP, the closely related dexamethasone was shown to induce senescence [17,18]. Another widely used drug, the opioid loperamide was also characterized as a senomorphic along with the antipsychotic fluspirilene and a number of dopamine and serotonin antagonists [9]. Finally, the already observed favorable effect of the antidiabetic metformin on lifespan extension was associated with a strong senomorphic action exerted by the biguanide derivative. Regarding the mechanistic aspects of metformin senotherapeutic effects, it was shown that SASP suppression was not directly related with AMPK kinase inhibition, a strong candidate mechanism for the antidiabetic action, but it was associated with inhibition of IKK, a different kinase upstream of NF-κB [19]. The fact that metformin is a well-tolerated drug combined with its potent effect

on delaying onset of age-related pathologies prompted the launch of a clinical study in collaboration with FDA, aiming at approval of additional indications for the drug [20].

A critical consideration of the current state of the art in the field of senotherapeutics points toward two opposing but not necessarily competing directions. On one hand, a remarkably sophisticated methodological machinery, including reverse pharmacology approaches, chemical biology techniques and advanced model systems has been utilized so far for the identification and mechanistic study of senolytic and senomorphic compounds. On the other hand, pure medicinal chemistry and early stage drug discovery efforts involving hit identification, hit-to-lead optimization and SAR derivation are awkwardly limited, in contrast to the fact that the first relevant molecular targets are already annotated, not to mention the multitude of already available drug-like modulators for many of those proteins. Present-day discoveries suggest an exceedingly promising potential for this area of therapeutics. By considering the demanding, iterative character of systematic medicinal chemistry studies and the time needed to bring such efforts to a complete success, we anticipate that in the near future a number of original drug-like scaffolds along with newly discovered drug targets will emerge, thus establishing medicinal chemistry-oriented development of senescence-targeting small molecules as one of the most attractive fields in the search for new therapeutics.

Acknowledgements

The author would like to thank the editors of the journal for their kind invitation and E Mikros for his critical reading of this manuscript.

Financial & competing interests disclosure

The author acknowledges financial support by the H2020-INFRADEV-01-2017 project EPTRI (777554). The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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