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RESEARCH HIGHLIGHT

IMMP2L: a mitochondrial protease suppressing cellular senescence

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Cellular senescence contributes to organismal aging and tumor suppression. A recent paper by Yuan et al. published in *Cell Research* now unveils that switching off a mitochondrial protease can simultaneously suppress phospholipid biosynthesis and lethal signaling for senescence induction.

Organismal aging is coupled to the accumulation of senescent cells that, by definition, are permanently arrested in their cell cycle and often manifest the senescence-associated secretory phenotype (SASP), hence favoring chronic tissue inflammation.[1] One prominent biomarker of cellular senescence is the enhanced expression of cyclin-dependent kinase (CDK) inhibitor 2A (CDKN2A, best known as p16). Genetic ablation of senescent cells by expressing inducible suicide genes under the control of the CDKN2A promoter can retard and reverse aging phenotypes in mice.[2] That said, the phenomenon of cellular senescence also has important physiological functions, for instance in the suppression of oncogenesis (by irreversible arrest of the cell cycle in potentially malignant cells) and in wound healing (presumably because the SASP can favor local tissue repair).[3]

Much of the research on senescence has focused on the tumor suppressor p53 protein (TP53)-dependent or -independent mechanisms leading to the activation of CDKN2A or other CDKs. In a recent paper in *Cell Research*, Yuan et al.[4] reveal the surprising finding that one major mechanism leading to senescence may consist in the shut down of inner mitochondrial membrane peptidase subunit 2 (IMMP2L), through downregulation of protein expression or inactivation by an endogenous clade B serine protease inhibitor named SERPINB4.[4] Indeed, in normal bronchial epithelial cells, induction of senescence by blockade of epidermal growth factor receptor was linked to the transcriptional upregulation of SERPINB4, and SERPINB4 knockdown could prevent senescence in this model, while its overexpression was sufficient to trigger senescence.[4] Similarly, knockdown of IMMP2L, which turned out to be the principal target of SERPINB4, stimulated the senescent program in various human cell types in vitro[4], echoing the prior observation that mice bearing a mutation in the *IMMP2L* locus display a progeroid (early aging) phenotype.[5] In the muscle from aged normal mice, as well as in peripheral blood from fragile old humans, IMMP2L was diminished (while CDKN2A protein was increased) as compared to young controls.[4] More importantly, deletions of intron 3 of *IMMP2L* were less frequent in centenarians than in unrelated control individuals, indicating that longevity is associated with genomic integrity of the *IMMP2L* locus[4]. All these findings argue in favor of the conjecture that organismal aging and cellular senescence are coupled to the downregulation or inhibition of IMMP2L (Fig. 1). It remains to be seen, however, whether transgene-enforced upregulation of IMMP2L or depletion/deletion of its inhibitor SERPIN4B may reduce the manifestations of aging in whole organisms. Moreover, it might be interesting to develop pharmacological inhibitors of the IMMP2L/SERPIN4B interaction to allow newly synthesized IMMP2L to escape from its irreversible blockade by SERPIN4B, thus reactivating its function.

By which mechanism can IMMP2L suppress senescence? Through a series of elegantly conducted experiments, Yuan et al.[4] demonstrate that, in non-senescent cells, IMMP2L assures the proteolytic maturation of two major substrates, namely glycerol-3-phosphate dehydrogenase 2 (GPD2), a metabolic enzyme, and apoptosis-inducing factor (AIF), a redox-active flavoprotein that contributes to the biogenesis of the respiratory chain complex I, but also has a potentially lethal function.[6,7]

After its processing by IMMP2L, GPD2 locates at the inner mitochondrial membrane where it catalyzes the conversion of glycerol-3-phosphate (G3P) to dihydroxyacetone phosphate (DHAP). Together with GPD1, GPD2 constitutes the glycerol phosphate shuttle, which reoxidizes NADH formed during glycolysis, coupling this reaction to the reduction of coenzyme Q (ubiquinone to ubiquinol), which enters into oxidative phosphorylation. Apparently, knockdown of GPD2 is sufficient to recapitulate many features of cellular senescence, phenocopying the effect of IMMP2L depletion.[4] GPD2 may have two effects on cellular metabolism that have anti-senescent effects. On one hand, it may increase NAD^+ levels, knowing that NAD^+ has prominent pro-longevity effects.[8] On the other hand, GPD2 may favor mitochondrial phospholipid synthesis by providing the precursor G3P. Indeed, the abundance of mitochondrial phospholipids and phospholipid-binding proteins such as protein kinase C-δ (PKC-δ) diminished upon depletion of either IMMP2L or GPD2. This effect was coupled to reduced phosphorylation of the PKC-δ substrate pyruvate dehydrogenase kinase (PDK), resulting in subsequent dephosphorylation and enhanced activity of the PDK substrate pyruvate dehydrogenase (PDH).[4] PDH favors the catabolism of pyruvate via the tricarboxylic acid cycle and has previously been implicated as a key effector of oncogene-induced senescence.[9] Altogether, this cascade illustrates how failed processing of one metabolic enzyme, GPD2, by IMMP2L can precipitate a cascade of

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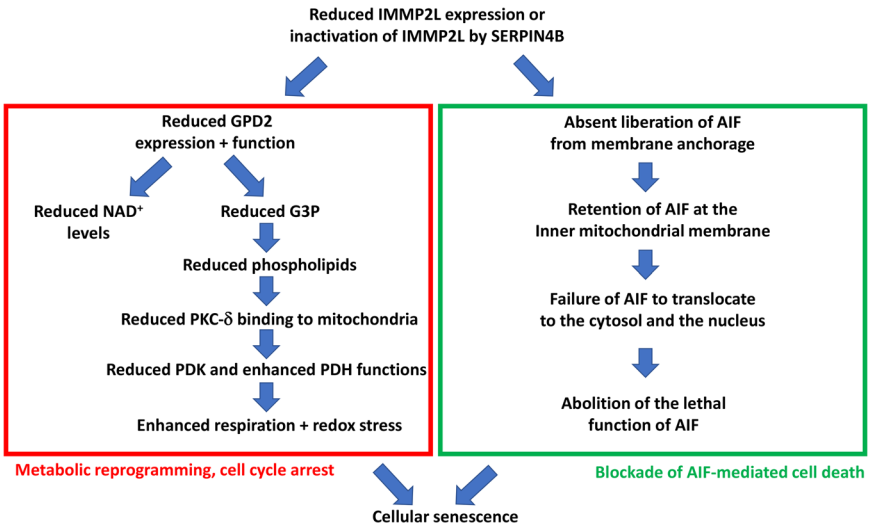

Fig. 1 Schematic overview of the pathway linking IMMP2L to senescence. Inactivation or inhibition of IMMP2L causes the inhibition of the expression and function of GPD2, thereby inducing metabolic reprogramming of the cell. Suppression of IMMP2L also leads to the selective inactivation of the pro-death function of AIF. Together, these alterations cause cellular senescence. The molecular links to the upregulation of CDK inhibitors and the SASP remain to be established

events that eventually culminates in the reprogramming of mitochondrial membrane composition and metabolic function, favoring the senescent phenotype (Fig. 1). It will be interesting to investigate whether external provision of NAD^+, G3P, or phospholipid precursors, as well as inhibition of PDH, might avoid or reverse the senescent phenotype in vitro or in vivo.

IMMP2L also catalyzes the proteolytic maturation of AIF. AIF is usually tethered to the inner mitochondrial membrane by its N terminus. This membrane-sessile form of AIF contributes to the biogenesis of the respiratory chain complex I[7,10] and catalyzes redox reactions.[11] Upon cleavage of its membrane anchor (yielding truncated AIF, tAIF) as well as outer mitochondrial membrane permeabilization, tAIF can translocate from the mitochondrial intermembrane space to the cytoplasm and the nucleus of cells to induce cell death.[12] This phylogenetically conserved pathway occurs in a caspase-independent fashion, coupling mitochondrial dysfunction to cellular demise, for instance in the context of oxidative stress-mediated cell death.[12] Yuan et al.[4] identify IMMP2L as a major AIF protease, facilitating the release of tAIF from mitochondria, hence contributing to its lethal function. Yuan et al.[4] suggest that the senescence-associated inactivation of IMMP2L might cause the suppression of the AIF-dependent cell death pathway, thus facilitating the long-term survival of senescent cells (Fig. 1). It will be interesting to study the phenotype of mice in which endogenous AIF is replaced by an IMMP2L-resistant, uncleavable mutant. If the pathway delineated by Yuan et al. was correct, such mice should manifest a higher incidence of senescent cells in their tissues.

Altogether, the landmark contribution by Yuan et al. unveils new mechanisms connecting cellular senescence to metabolism and cell death signaling pathways. It remains to be seen whether these novel pathways furnish new actionable targets for intervening on age-associated diseases.

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