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Plasma membrane damage is a new trigger of cellular senescence

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Abstract

Cellular senescence, by blocking proliferation and inducing a secretory phenotype, has beneficial and deleterious effects, the latter being linked to aging. Suda, Moriyama, Razali, *et al.* recently reported that plasma membrane damage (PMD) triggers senescence, suggesting that PMD inducers promote senescence and that the PMD repair machinery can regulate it.

Cellular senescence results in proliferation arrest and the production of a senescence-associated secretory phenotype (SASP), sending signals to the microenvironment. When timely regulated, senescent cells have beneficial effects on organismal physiology (e.g., during embryogenesis and wound healing). However, when they accumulate, they contribute to aging and its associated diseases, making the manipulation of senescent cells an emerging strategy to improve healthy aging. Senescent phenotype can be induced by signals and stresses such as genotoxic drugs, telomere shortening, oncogene activation, mitochondrial stress and ROS production, which lead to DNA damage and p53 activation contributing to senescence [1]. Still, other signals, in particular in the context of physiological senescence, could trigger it. For instance, during development, TGF β proteins could participate in senescence, and TGF β -induced senescence through pathways that may be independent of DNA damage [2,3]. A better understanding of the mechanisms promoting senescence is critical to better apprehend contexts where exposure/stresses/signals promote senescence in different pathophysiological conditions, and to identify novel mechanisms contributing to senescence, especially for physiological senescence where little is known.

The plasma membrane (PM) insulates cells from their microenvironment, which is essential for cell function and survival. PM damage (PMD) can be induced by intra- and extra-cellular signals/stressors (e.g., ROS, radiation, migration, physical stresses or pathogens) in normal and pathological situations. To avoid cell death or to prevent subtoxic damage induced by the release of cytosolic material and exposure to outside materials during the PM wound, efficient repair mechanisms can resolve the damages. However, persistent PMD is implicated in many pathological situations including neurodegenerative diseases, cardiovascular diseases and cancers [4,5], reminiscent of diseases involving senescent cells.

Recently, Suda, Moriyama, Razali, *et al.* [6] reported that non-lethal PMD shortens yeast replicative lifespan and triggers cellular senescence in normal human fibroblasts. The

authors started by defining a simple and universal method to provoke PMD using sodium dodecyl sulfate (SDS). Using this method, a genome-wide screen performed on yeast revealed 48 mutants displaying increased sensitivity to PMD that could be classified into different functional groups, including a group with dysfunctional endosomal sorting complex required for transport (ESCRT) critical for PMD response [7]. Strikingly, several yeast mutants of the ESCRT group displayed a shortened replicative lifespan, whereas their overexpression extended lifespan, supporting that the machinery to repair PMD impacts physiological replicative lifespan in yeast. Importantly, similar results were obtained in normal human fibroblasts. Indeed, SDS and other PMD inducers limited the replicative potential by inducing premature senescence, characterized by the presence of classical hallmarks: increased expression of p16 and p21 cyclin-dependent kinase inhibitors, loss of replication, increased SA- β -galactosidase activity and increased expression of SASP components IL6 and CCL2. In addition, spots of externalized phosphatidylserine (PS), a mark of PMD, were detected during replicative senescence and PMD-induced senescence. In the latter case, the ESCRT component CHMP4B localized to these spots and its expression rescued PMD-induced senescence. Nevertheless, whether CHMP4B or other components promoting PMD repair could increase the replicative potential of human fibroblasts was not described.

Calcium influx is an early event following PMD [7], and calcium fluxes and signaling have recently emerged as critical regulators of cellular senescence [8,9]. This influx of calcium might play a role in PMD-induced senescence as calcium chelation was shown to decrease most of the senescence hallmarks examined, except for p16 and CCL2 that were not impacted. PMD could thus regulate senescence through calcium-dependent and -independent signaling. Accordingly, inducing a calcium influx by KCl treatment was sufficient to induce premature senescence, as previously observed [10]. Still, in this context, p16 was induced suggesting that calcium signaling induced by PMD or by KCl are not identical, particularly for p16 regulation.

This calcium influx activated the p53 pathway, a pathway often involved in senescence induction, and p53 was shown to mediate PMD-induced senescence as p53 knockdown inhibited it. How calcium influx activates the p53 pathway remains largely unknown. DNA damage, a classical upstream activator of p53, does not seem to be activated during PMD-induced senescence and inhibition of the DNA damage response pathway did not prevent p53 pathway activation, supporting that calcium activates p53 independently of DNA damage. Still, yeast mutants in the DNA replication/damage/repair group were, like the ESCRT group, more sensitive to PMD, supporting a potential link between DNA damage and PMD, at least in yeast. Additional studies will be required to decipher the connection between calcium, DNA damage and p53 in the response to PMD.

Comparison of the transcriptomic profiles of senescent cells induced by PMD or by other inducers suggests that PMD triggers classical senescence-associated gene signatures, including cell cycle and SASP features, albeit the kinetics of senescence might be slower in the context of PMD. The authors also observed that the PMD-induced SASP might be closer to the SASP associated with wound healing than to the SASPs induced by other triggers, and that it is functionally more efficient at promoting cell migration than other SASPs.

The work of Suda, Moriyama, Razali, *et al.* constitutes a first critical step that opens avenues of research to better understand cellular senescence state and its role in different pathophysiological contexts (Figure 1). The discovery that PMD can trigger senescence raises the possibility that PMD inducers, so far not associated with the induction of cellular senescence, might constitute a novel class of senescence inducers (e.g., shear stress and other mechanical forces, migration, pore-forming toxins, bile acids, some proteases). This could have some implications for PMD-associated disorders: senescence could play a role in diseases such as Scott syndrome, and PMD could promote the senescence reported for example in muscular dystrophy. The findings of the authors also suggest that many known inducers of senescence

thought to act through DNA damage, and also known to provoke PMD independently of DNA damage, could also trigger senescence through PMD (e.g., tobacco, asbestos, ROS, radiation). Externalized PS spots could be used as a readout to identify senescence linked to PMD and could be a hallmark of some senescence contexts. Further investigations into these aspects should help to better delineate signals and stresses promoting senescence in very different senescence contexts and pathophysiological conditions such as senescence induced during embryonic development, wound healing, or response to pathogens in particular viral infections. In this context, testing known PMD inducers for their ability to promote premature senescence and exploring PMD participation in physiological senescence (e.g., replicative senescence, oncogenic stress-induced senescence, oxidative stress-induced senescence) is needed. In addition, response of different cells types (e.g., epithelial and endothelial cells) to PMD-induced senescence would complete the work by Suda, Moriyama, Razali, *et al.* who used only human fibroblasts. This study also raises new hypotheses for some senescence features, such as the well-known cell swelling generally observed in senescent cells and that could result from osmotic changes due to uncontrolled exchange of ions and other materials through PMD. The authors show that the ESCRT machinery and/or calcium are involved in the regulation of yeast and human fibroblast replicative potential. It is essential to continue this work to better understand the role of this repair machinery as it might be involved in many senescence contexts (is PM repair machinery downregulated in different senescence contexts?) and its components might constitute new targets to manipulate senescent cells and impact senescence-related diseases, a major on-going challenge [11,12].

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DECLARATION OF INTERESTS

The authors declare no conflicts of interest.

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Figure legend

Fig. 1. A novel trigger of senescence: plasma membrane damage (PMD). Different types of stresses (chemical, physical, microbial or immune stress) trigger perturbation of the plasma membrane causing plasma membrane damage (PMD), which results in an early calcium (Ca^{2+}) influx into the cytosol. On the one hand, Ca^{2+} leads to the downstream activation of p53 which further activates p21 and IL6, important effectors of the stable cell cycle arrest and the senescence-associated secretory phenotype (SASP), respectively, the major features of cellular senescence. On the other hand, Ca^{2+} is involved in the PMD repair machinery, as well as the ESCRT-III complex, contributing to senescence regulation. Ca^{2+} -independent effects are also induced by PMD and may be responsible for p16 and CCL2 expression, other important effectors of senescence. The discovery of PMD-induced senescence offers new perspectives in pathophysiological contexts, as Suda, Moriyama, Razali, *et al.* proposed for wound healing. Stressors used in the Suda, Moriyama, Razali, *et al.* paper are represented in red; known senescence triggers that may play a role in PMD-induced senescence are represented in blue; known PMD triggers with no reported functions in senescence are represented in purple. This figure was created with BioRender.com.

