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► **To cite this version:**

Corinne Abbadie, Olivier Pluquet. Unfolded Protein Response (UPR) Controls Major Senescence Hallmarks. *Trends in Biochemical Sciences*, 2020, 45 (5), pp.371 - 374. 10.1016/j.tibs.2020.02.005 . hal-03490330

HAL Id: hal-03490330

<https://hal.science/hal-03490330>

Submitted on 22 Aug 2022

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1 **UNFOLDED PROTEIN RESPONSE (UPR) CONTROLS MAJOR**
2 **SENESCENCE HALLMARKS**

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14 **Running title:** UPR and senescence

15 **Abstract**

16 Senescence is a complex cellular state which can be considered as a stress response phenotype.
17 However, the mechanisms through which cells acquire and maintain this phenotype are not
18 fully understood. Here, we argue that the Unfolded Protein Response (UPR) may represent a
19 signalling platform that is associated with the major senescence hallmarks.

20

21 **Keywords (up to 6) :**

22 Senescence, Endoplasmic reticulum, Unfolded Protein Response, secretome, metabolism,
23 proteostasis

24 Senescence is a cellular state characterized by a stable proliferation arrest and accompanied by
25 molecular changes, including epigenetic changes, changes in membrane lipid composition,
26 increased oxidative stress, persistent DNA damage, increase in autophagic activity, and
27 metabolic reprogramming, as well as substantial morphological changes, such as cell
28 enlargement. Remarkably, senescent cells secrete a wide array of proteins constituting the so-
29 called senescence-associated secretory phenotype (SASP) which is enriched in pro-
30 inflammatory cytokines, growth factors, and enzymes remodelling the extracellular matrix.
31 Senescence can be induced by various types of stress, including telomere shortening, oxidative
32 stress, exposure to radio- or chemotherapy, UV radiation, and activation of oncogenes [1].
33 Therefore, senescence can be regarded as an adaptive response to stress. Upon stress, cells
34 trigger dynamic signalling pathways, including the unfolded protein response (UPR) elicited
35 by the endoplasmic reticulum (ER). We and others have shown that ER stress/UPR activation
36 occur at senescence [2]. Here, we discuss how these processes contribute to the senescent cell
37 specific properties.

38

39 **Evidence of altered ER homeostasis during senescence**

40 The ER plays a key role in proteostasis and controls much of the membrane proteome and
41 secretome. When ER homeostasis is disturbed by intrinsic and/or extrinsic stress, the UPR is
42 induced as an adaptive response. It is initiated by the activation of three sensors (PERK, ATF6 α ,
43 and IRE1 α), which results in the induction of their effectors in order to counteract the
44 proteostasis imbalance (**Box 1**). Different cell types undergoing senescence upon different
45 kinds of stress display structural alterations of the ER and elicit the UPR activation. For
46 example, dermal fibroblasts undergoing replicative senescence (RS) and melanocytes
47 undergoing oncogene (HRAS)-induced senescence (OIS) present enlarged ER and the
48 activation of the three arms of the UPR [3][4]. Lymphoma cells undergoing therapy-induced
49 senescence (TIS) have disorganized rough ER cisternae and the activation of at least the
50 IRE1 α /XBP1 and PERK/ATF4 branches of the UPR [5]. However, other reports indicate that
51 the UPR arms can be involved in senescence in a more differential manner. For example, in
52 HRAS-driven senescent keratinocytes, IRE1 α , but not PERK, was activated, and the IRE1 α
53 capacity to induce senescence implicated its RNase activity independently of XBP1 splicing
54 but through cleavage of *ID1* messenger RNA (mRNA) [6]. These few studies highlight that the
55 UPR could be a major basic mechanism on which the senescent phenotype relies, however with

56 some subtleties and specificities in the involvement of the numerous complex UPR
57 subpathways.

58

59 **Evidence that UPR controls several senescence hallmarks**

60 Since the UPR is activated at senescence, the questions are whether and how it contributes to
61 the establishment or maintenance of the specific properties/markers of senescent cells. First of
62 all, we and others reported that ER stress/UPR inducers (e.g. thapsigargin, dithiothreitol and
63 UV) applied to proliferating cells induce all major senescent hallmarks (e.g. SA- β -Gal activity
64 and DNA damage) [3][7]. However, converse approaches of invalidating the main UPR sensors
65 or effectors in already senescent cells have given a more nuanced picture. For example,
66 silencing ATF6 α , IRE1 α , or PERK in replicative senescent fibroblasts failed to alleviate the
67 senescent cell cycle arrest [3]. In contrast, silencing PERK and ATF6 α , but not IRE1 α , in
68 senescent keratinocytes, whose senescence is oxidative stress-dependent, significantly restored
69 their proliferation [8]. In HRAS-induced senescence, the control of the cell cycle arrest by the
70 UPR pathway is time-dependent. Indeed, HRAS activation induces hyperproliferation in the
71 first one or two days, followed by senescence within five to ten following days. Knocking-
72 down IRE1 α reduced proliferation of the first phase, and blocked the induction of senescence
73 and sustained proliferation during the second phase. This activity was shown to be independent
74 of *Xbp1* splicing since XBP1 knock-down blocked proliferation and accelerated senescence [6].

75 The senescent cell cycle arrest is mainly the result of the persistence of unrepaired DNA
76 damage. Interconnections between DNA damage/repair and ER stress/UPR in the context of
77 senescence were, up to now, poorly investigated. However, based on transcriptomic profiling,
78 a recent study predicted that ATF4, one component of the PERK pathway, might play a role in
79 DNA damage repair during senescence [9]. Another obvious *in vitro* senescence marker is the
80 increase in cell size and spreading. We have shown that the silencing of ATF6 α , and
81 ATF6 α only, in replicative senescent fibroblasts reduced cell spreading and restored a fusiform
82 shape similar to that of exponentially growing fibroblasts. Interestingly, these effects were
83 correlated with reversed ER expansion [3].

84 The third widely recognized marker of senescence is the senescence-associated β -
85 Galactosidase (SA- β -Gal) activity, reflecting the increase in lysosome and autophagic vacuole
86 content. According to the cell type and senescence inducer, invalidation experiments
87 highlighted either ATF6 α and IRE1 α , or ATF6 α and PERK as the main factors responsible for
88 increased SA- β -Gal activity [3][4][7][8]. Accordingly, silencing of ATF4 (PERK effector) in

89 TIS glioblastoma cells significantly decreased the level of MAP1LC3-II, which is indispensable
90 to the autophagic activity [10].

91 Finally, regarding the SASP, a study indicated that ER stress may trigger a negative
92 feedback loop attenuating the SASP gene expression [11], suggesting that ER stress/UPR
93 activation might have an impact on the secretome composition. It was also shown that the
94 increased demand for protein synthesis to ensure the SASP component production during
95 HRAS-mediated senescence induces a proteotoxic stress and UPR activation [5][11].

96 These above-mentioned results raise the question of whether UPR is the cause or the
97 consequence of senescence. The answer is probably that both are true because of additional
98 layers of auto-amplification loops. Therefore, determining the temporal sequence of the cause-
99 effect relationship between UPR and senescence will be the next challenge in the field. Another
100 pending question is whether the proteotoxic stress (due to oxidized misfolded protein or SASP
101 protein overload) is the only mechanism that induces/maintains UPR at senescence.
102 Interestingly, changes in membrane lipid composition occur during senescence [12] and
103 structural changes of the ER lipids can directly activate the ATF6 α and IRE1 α /XBP1s UPR
104 arms. These two pathways, in turn, are known to activate lipid biosynthesis [13], indicating an
105 interdependency between lipids and UPR, both of which may lead to cellular senescence
106 independently of proteotoxic stress. Overall, these data support the hypothesis that UPR is a
107 signalling platform associated with senescence hallmarks (**Figure 1**).

108

109 **Modulating UPR to limit senescence and age-related diseases**

110 Senescent cells accumulate during aging in most tissues and organs. Eliminating these
111 senescent cells using a dedicated mouse model or senolytic drugs (drugs able to kill senescent
112 cells) increased life span and decreased the incidence of most age-related pathologies [14]. The
113 UPR is established as a survival mechanism enabling cells to resist and resolve stress, but also,
114 when sustained because of a stress that remains unresolved, as a mechanism leading to cell
115 death by apoptosis, mainly through the activation of the CHOP transcription factor [15]. In
116 senescent cells, the UPR is activated in a long term, and CHOP is often activated
117 [3][4][5][8][10][11], but, surprisingly, does not lead to senescent cell death. Therefore,
118 senescent cells might require an optimal UPR activity (specific subpathways at specific levels
119 of activation with specific kinetics) for their long-term survival. If this is true, pharmacological
120 compounds inhibiting the UPR subpathways might act as senolytics. However, none of the
121 above cited studies where some UPR pathways were invalidated led to this conclusion. In
122 contrast, they have shown that invalidating the UPR led to a regression of the senescent

123 hallmarks. Therefore, inhibiting some of the UPR sensors or effectors (e.g. ATF6 α in
124 replicative senescence or IRE1 α in Hras-driven senescence) by specific pharmacological
125 compounds could be beneficial to delay, limit, or even suppress the deleterious aspects of
126 senescence, in particular the inflammatory SASP. Hence, they would work as senomorphics,
127 i.e. drugs able to suppress all or part of deleterious senescence hallmarks, and which could have
128 less detrimental secondary effects than senolytics. Of course, further *in vivo* experiments are
129 needed to better understand this therapeutic potential.

130

131 **Acknowledgements**

132 This work was supported by a grant from CPER Longevity (granted to O.P) and two grants
133 from the French Ligue Contre le Cancer (from Comité du Nord to O.P. and from Comité de la
134 Somme to C.A.).

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172 **Box 1: Activation of the three arms of the UPR pathway**

173 The UPR acts through three sensors: PERK, IRE1 α and ATF6 α . The PERK kinase reduces cap-
174 dependent protein synthesis through eIF2 α phosphorylation, and induces the transcription of
175 genes encoding specific chaperones by activating the ATF4 transcription factor. Activated
176 IRE1 α induces unconventional splicing of the XBP1s mRNA which gives rise to an active
177 transcription factor whose main targets are the genes whose products are involved in the quality
178 control of the ER proteins. Other mRNAs are cleaved by IRE1 α in a process called Regulated
179 IRE1 α -dependent decay (RIDD). However, the physiological consequences of this mechanism
180 are not yet fully known. ATF6 α , upon activation, exits the ER and integrates the Golgi
181 apparatus membrane where it is cleaved by the Site-1 protease (S1P) and Site-2 protease (S2P)
182 to its active form which acts as a transcription factor targeting genes encoding chaperones
183 (Figure 1). If the cell adaptation through UPR is not possible due to prolonged or unresolved
184 ER stress, cell death can be induced through the IRE1 α /JNK or the ATF4 pathways.

185 **Figure 1: Interconnection between UPR and senescence**

186 All three ER stress sensors (PERK, IRE1 α , and ATF6 α) activate signaling events that lead to
187 the attenuation of protein synthesis as well as to the induction of a specific transcriptional
188 program both aiming to restore ER proteostasis and more broadly cellular homeostasis. Some
189 of the UPR downstream signaling events, yet unknown, control the establishment and/or
190 maintenance of the main senescence hallmarks including cell cycle arrest, DNA repair capacity,
191 morphological changes, metabolic changes, the secretory pathway, and changes in membrane
192 lipid composition. Arrows, positive regulation; Dead end arrow, negative regulation; JNK, c-
193 Jun N-terminal kinase ; S1P/S2P, Site-1/2 protease; P, phosphorylation; ATF4, Activating
194 Transcription Factor 4; XBP-1s, spliced form of X-box binding protein 1.

