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Review

Aberrant signaling and senescence associated protein degradation

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ABSTRACT

Senescent cells accumulate with age and contribute to pathologies associated to old age. The senescent program can be induced by pro-cancer stimuli or is developmentally controlled. In cells forced to senesce by expression of oncogenes or short telomeres, aberrant activation of the ERK/MAP kinase signaling pathway leads to selective protein degradation by the ubiquitin proteasome system. The proteins affected by this process control key cellular processes known to be defective in senescent cells. We discuss the evidence supporting a general role for aberrant signaling and senescence associated protein degradation for organismal aging.

Contents

1. Introduction

Organisms progressively decay, wear out and die. However, the primary causes triggering these processes have been largely elusive. At the cellular level, cells can die or senesce and the mechanisms of these cellular fates can give insights into organismal aging. Cellular senescence can be greatly accelerated by oncogenic signaling which is different from normal signaling in strength and response to negative modulators. Oncogenic signaling is thus aberrant signaling. Oncogenic *ras*, for example, activates the ERK and AKT kinases leading to the phosphorylation of multiple proteins. Using proteomics analysis, we found that aberrant ERK signaling due to expression of oncogenic *ras* or short telomeres leads to degradation of specific proteins (Deschenes-Simard et al., 2013). Most of the degraded proteins contained phosphorylation motifs for proline directed kinases such as ERK1, ERK2, CDKs and GSKs. These kinases are stimulated by oncogenic *ras* or short telomeres and provide a direct link between senescent stimuli and protein degradation. In addition, many unstable proteins in senescent cells were found to contain phosphorylation sites for basophilic kinases such as AKT and S6 kinase or acidophilic kinases such as casein kinases 1 and 2. These kinases could be stimulated as a consequence of signaling by Ras-activated kinases. Alternatively, ERK-dependent production of reactive oxygen species can enhance overall protein phosphorylation due to inhibition of protein phosphatases (Meng and Zhang, 2013). The proteins degraded in senescent cells play roles in cell cycle progression, ribosome biogenesis, cell migration, mitochondria and other functions known to be affected in these cells (Deschenes-Simard et al., 2014).

The stoichiometry of most phosphorylation events indicates that only a fraction of a particular protein is phosphorylated (Olsen et al., 2010). Therefore, during normal cell signaling the coupling between protein phosphorylation and degradation will only impact a fraction of any particular protein pool. However, during aberrant signaling, as in cells bearing constitutively active oncogenes, a larger fraction of some

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particular proteins will be phosphorylated and subsequently degraded. We call this process Senescence Associated Protein Degradation or **SAPD** (Deschenes-Simard et al., 2013) and for some proteins it dominates over their biosynthesis, significantly reducing their overall levels. This mechanism is independent of cell division and could in principle explain cell dysfunctions for both dividing and non-dividing cells exhibiting aberrant signaling. However, currently the term cellular senescence applies only to dividing cells, although the process could be logically extended to non-dividing cells based on molecular instead of cellular phenotypes. Hence, non-dividing cells exhibiting dysfunctions due to the senescence associated secretory phenotype (SASP) (Oubaha et al., 2016) and SAPD could be classified as senescent.

Oncogenic mutations are not linked to normal aging but senescent cells accumulate with age in many organisms including humans (Childs et al., 2015; Tchkonia et al., 2013). On the other hand, cells could senesce in vivo in response to still unknown factors triggering aberrant signaling and SAPD (Fig. 1). The SAPD model of senescence includes: 1) a cause for aberrant signaling, 2) coupling protein modifications induced by aberrant signaling to protein degradation and 3) the cellular consequences of depletion of SAPD target proteins. Here, we review the evidence that links aging and the SAPD model.

2. Aberrant signaling during aging

Signaling includes a variety of protein modifications including phosphorylation, acetylation, methylation and sumoylation. These modifications may all contribute to aging but here we focus on protein phosphorylation which is the best understood. There is an extensive body of work on protein acetylation and aging, a pathway controlled by the protein deacetylases of the sirtuin family, which has been reviewed elsewhere (Haigis and Sinclair, 2010) and will not be included here.

2.1. Model organisms

Genetic analysis of aging in model organisms has lead to the identification of kinases that shorten life span. In *C. elegans* the insulin/IGF-1 signaling activates the PI3K/AKT cascade leading to phosphorylation and cytoplasmic sequestration of the forkhead transcription factor Daf-16 (Paradis and Ruvkun, 1998). This transcription factor is a key mediator of longevity in worms and it regulates the expression of genes that can increase resistance to a variety of cellular stresses (Lee et al., 2003). Intriguingly, Daf16 also acts as a transcriptional repressor of many protein kinase genes including those that inactivate its own function (Tazearslan et al., 2009). This striking attenuation of many kinase-signaling modules included the PI3 kinase pathway, the TOR pathway and the ERK/MAP kinase pathway (Tazearslan et al., 2009). Clearly, protein phosphorylation is linked to aging and its attenuation increase life span (Fig. 1).

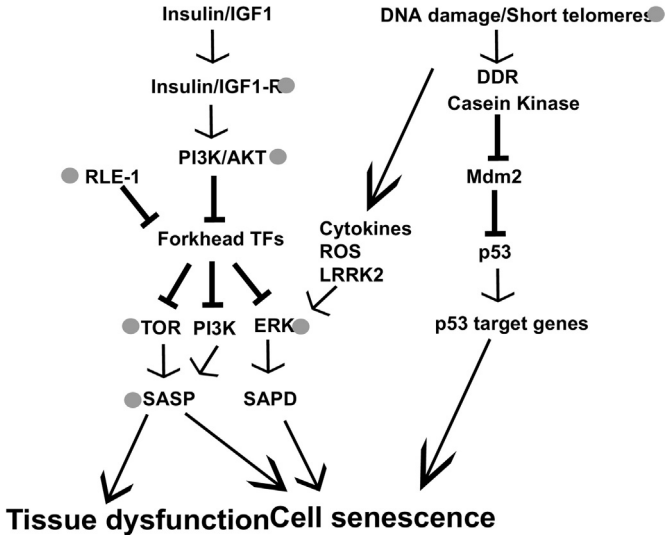

Fig. 1. Aberrant signaling underlies cell senescence and aging. Aberrant activation of signaling pathways due to triggers that remain to be discovered reduce cellular fitness in part by promoting protein degradation (SAPD) and reducing tissue homeostasis via the secretion of high levels of inflammatory cytokines (SASP). In cell culture and animal models, short telomeres, oncogenes and DNA damaging drugs can mimic the process. In animal models, mutations or compounds that reduce signaling through the PI3K, AKT, ERK and TOR kinases or prevent DNA damage signaling increase life span (gray circle).

Consistent with the work in worms, inhibitors of the ERK pathway (Slack et al., 2015) or mutations in the PI3K/AKT pathway (Yamamoto and Tatar, 2011) also prolonged life span in flies. Moreover, in agreement with the idea for a pro-longevity role for kinase attenuating mechanisms, fibroblasts obtained from long-lived mutant mice, including the Snell dwarf mice and the Growth Hormone Receptor mutant mice, displayed an attenuated ERK activation in response to oxidative stress (Sun et al., 2009).

Another protein kinase that has pro-aging functions is casein kinase 1 (Fig. 1). This kinase is controlled by the proteasome activator REGγ. Mice null for REGγ accumulate CK1, which then phosphorylates Mdm2, targeting it for proteasome-dependent degradation (Inuzuka et al., 2010). As a result, these mice experience an increase in p53 levels and activity and premature aging (Li et al., 2013). CK1 is activated by DNA damage and colocalize with p53 in PML bodies where it phosphorylates p53 at threonine 18 an event that prevents its interaction with Mdm2 (Alsheich-Bartok et al., 2008). Signs of CK1 activation in Alzheimer disease also suggest a role for this kinase in human aging (Flajolet et al., 2007; Hanger et al., 2007).

2.2. Human aging

Aberrant phosphorylation of the neuronal cytoskeleton by ERK kinases or decrease in phosphatases is associated to brain aging and human Alzheimer disease (Veeranna et al., 2004; Veeranna et al., 2011). MEK inhibitors prevent memory deficits in a mouse model of Alzheimer disease (Feld et al., 2014). The Raf-1 kinase, which acts upstream ERK1/2 in the MAPK pathway, is also increased in the brain of Alzheimer disease patients (Mei et al., 2006), and treatment with Raf kinase inhibitors protects cortical brain cells from β-amyloid toxicity (Echeverria et al., 2008). Raf inhibitors also reduced mutant huntingtin toxicity in a cell model of Huntington disease where RNAi-mediated inhibition of multiple members of the RAS-RAF-ERK pathway rescue cells and animal models form this toxicity (Miller et al., 2012). GSK3b is another kinase that can phosphorylate the cytoskeletal protein tau in neurons from patients with Alzheimer disease (Noble et al., 2005). This kinase increases with aging in the brain and accumulates in the nucleus of senescent fibroblasts (Zmijewski and Jope, 2004). The most common genetic mutation leading to Parkinson disease affects the protein kinase LRRK2, and most of its effects can be explained by activation of the ERK pathway (Fig. 1). Treatment with MEK inhibitors reversed most of the phenotypic effects of this mutation in neuron cultures (Bravo-San Pedro et al., 2013; Carballo-Carbajal et al., 2010; Reinhardt et al., 2013; White et al., 2007). As reported for Alzheimer disease, a reduction in protein phosphatase 2A activity can also underlie an aberrant protein phosphorylation state in Parkinson disease (Wu et al., 2012).

According to the SAPD model attenuation of kinase signaling should extend life-span by preventing the conversion of signaling pathways from a state of moderate signaling to a state of aberrant signaling leading to protein inactivation by SAPD (Fig. 1). Organisms need to use these signaling modules for cell proliferation and growth and they are in constant danger of passing the threshold for aberrant signaling, SAPD and senescence. A trade must be reached and longer life span can be achieved by attenuating signaling pathways. However, there is a fitness cost associated to lower activity that depends on the environmental pressures and the competition within species to pass genes to the next generation.

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