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opinion

To aggregate or not to aggregate? A new role for p62

Cell signalling is carried out by selective and complex metabolic networks that, when impaired, result in disease. The challenge for the cell is to maintain fidelity during normal processes, while allowing the plasticity that is required to control the complicated machinery of a functional cell. This is achieved through protein hubs that organize the flow of information inside the cell; one such hub is the signalling adapter p62 (Moscat *et al*, 2006). The identification of p62-interacting proteins, the analysis of knockout (KO) mice, and the fact that p62 mutations are associated with a human disease—Paget bone disease—have confirmed the importance of p62 in homeostatic cell function and disease (Moscat *et al*, 2007). p62 binds to atypical PKCs, the signalling adapter RIP, the E3 ubiquitin ligase TRAF6, the kinase ERK, and caspase 8 through different motifs (Jin *et al*, 2009; Moscat *et al*, 2006), thereby eliciting various effects that have been confirmed phenotypically in p62 KO mice. These include alterations in bone physiology, metabolic control and adipogenesis, T lymphocyte function and resistance to cancer (Moscat *et al*, 2007). p62 is localized in cytoplasmic speckles, where it concentrates and oligomerizes polyubiquitinated signalling proteins to facilitate the efficient activation of pro-survival and pro-apoptotic pathways (Jin *et al*, 2009; Moscat *et al*, 2006). This way, p62 emerges as a crucial factor in normal homeostasis and cancer, depending on the specific stimulus and possibly other conditions (Duran *et al*, 2008).

p62 is a target of autophagy (Komatsu *et al*, 2007), which might modulate the signalling pathways emanating from p62 speckles in metabolically stressed cells. When autophagy is inhibited, p62 speckles become bigger p62-containing aggregates that co-localize with polyubiquitinated, presumably misfolded proteins that are normally degraded by autophagy (Komatsu *et al*, 2007). A similar pattern is detected in cells in which the proteasome is inhibited, which has led to the hypothesis that the role of p62 under these conditions is to aggregate polyubiquitinated proteins—which can be toxic when soluble—into harmless 'packages'. When these polyubiquitinated aggregates are formed as a consequence of proteasome inhibition, p62 could deliver them to the autophagosome for degradation. Thus, in addition to its role as a signalling hub, p62 could function in 'garbage packing' and the eventual disposal of toxic proteins. However, there are several concerns with this proposed role for p62 that need to be addressed. One question is teleological: if the role of p62 is to deliver 'packaged' toxic proteins for degradation through autophagosomes, why is p62 itself degraded? It does not make 'economical' sense for the cell to degrade the package and also to kill the delivery guy. Another intriguing question originates from the fact that increased levels of p62 in autophagy-deficient cells inhibit the proteasome, leading to the enhanced accumulation of polyubiquitinated proteins as aggregates (Korolchuk *et al*, 2009). This suggests that, in cells that are deficient in both autophagy and p62, the lack of aggregates is not due to the absence of p62-mediated protein packaging but, rather, because p62 deficiency leads to enhanced proteasome activity, which degrades polyubiquitinated proteins before they can accumulate. A third concern is the toxicity phenotype of the *Atg7/p62* double KO mice, as compared with *Atg7* KO mice, which is not consistent with the purported role of p62 in alleviating the toxicity of soluble polyubiquitinated proteins. If the role of p62 is to concentrate the toxic proteins into aggregates, the loss of p62 should worsen liver toxicity in the *Atg7* KO mice; however, the published evidence is contrary to this idea, as the livers of *Atg7/p62* double mutants are healthier than the *Atg7* KO livers (Komatsu *et al*, 2007).

A recent study surprisingly reported that the mTOR small GTPase regulator Rheb is a key molecule in the control of aggresome formation and the metabolism of misfolded proteins (Zhou *et al*, 2009). The hyperactivation of Rheb in proteasome-inhibited cells leads to increased cell toxicity and reduced aggresome formation, independently of mTOR (Zhou *et al*, 2009). These findings are consistent with the idea that aggregate formation prevents cell toxicity but are at odds with the liver phenotype of the *Atg7/p62* double KO mice (Komatsu *et al*, 2007). A better characterization of the nature and role of the different aggregates that are formed during autophagy and proteasome inhibition would help to clarify their physiological role in cell pathology.

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