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AUTOPHAGY

STAT3 maintains order

Rubber ball

Autophagy has a vital role in cell homeostasis and coordinates multiple aspects of the cellular response to stress stimuli. Here, Shen *et al.* identify a novel mechanism of autophagy repression that involves pro-inflammatory signalling.

The authors identified pharmacological inhibitors of STAT3 (signal transducer and activator of transcription 3; which is involved in inflammation) as potent activators of autophagy in a library screen for autophagy inducers. Small interfering RNA (siRNA)-mediated knockdown and overexpression of STAT3 confirmed its role in this process and showed that cytoplasmic STAT3, rather than nuclear STAT3, regulates autophagy. Similarly, hallmarks of autophagy, including enhanced eukaryotic translation initiation factor 2α (eIF2α) phosphorylation and increased relocalization of endogenous LC3B into cytoplasmic puncta, were observed in mouse embryonic fibroblasts (MEFs) lacking hepatic *Stat3*.

Previous work had identified STAT3-interacting proteins as modulators of autophagy, including PKR, an eIF2α kinase that has been implicated in viral autophagy and endoplasmic reticulum stress. The authors found that STAT3 inhibition consistently increased the activity of PKR but not the activity of other interacting proteins. Co-immunoprecipitation assays revealed that STAT3 specifically binds to PKR when autophagy is off, and that this interaction is decreased in response to autophagic stimuli, such as STAT3 inhibitors and starvation.

So, what is the functional role of this interaction? Using STAT3 mutants, the authors determined that this direct association involves the STAT3 SH2 domain, which resembles the catalytic domain of the PKR substrate eIF2α, suggesting that STAT3 prevents autophagy by inhibiting the enzymatic activity of PKR. Indeed, STAT3 inhibition increased eIF2α phosphorylation in U2OS cells, an effect that was not seen in the absence of PKR. Moreover, STAT3-deficient MEFs had increased levels of phosphorylated eIF2α, whereas MEFs carrying a non-phosphorylatable eIF2α showed a reduced autophagic response in the presence of STAT3 inhibitors compared with wild-type cells. In addition to STAT3 inhibitors, saturated fatty acids, such as palmitate, could induce dissociation of STAT3 and PKR and activate autophagy, an effect that was abolished by STAT3 overexpression. This suggests that STAT3 functions as a negative regulator of autophagy in physiological conditions.

The authors propose a mechanism by which cytoplasmic STAT3 inhibits autophagy in a transcription-independent manner by directly interacting with PKR, and they suggest that this association is disrupted by physiological autophagy inducers.

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ORIGINAL RESEARCH PAPER Shen, S. *et al.* Cytoplasmic STAT3 represses autophagy by inhibiting PKR activity. *Mol. Cell* 18 Oct 2012 (doi:org/10.1016/j.molcel.2012.09.013)