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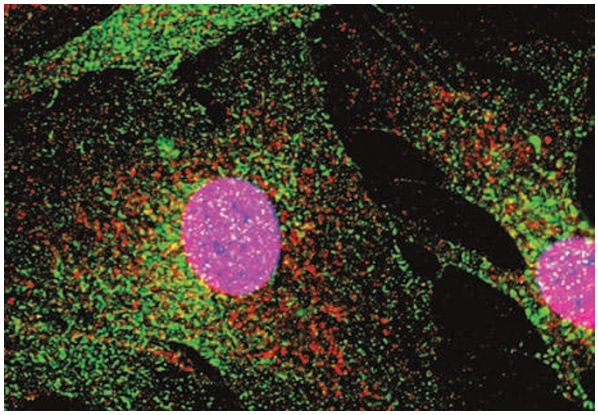
AUTOPHAGY

In the hands of HMGB1

> a crucial new player in the ever-growing group of proteins that control autophagy

Autophagy is a lysosomal degradative pathway that results in the engulfment and degradation of cytoplasmic contents in response to nutrient starvation or metabolic stress. A study by Tang *et al.* provides evidence that high mobility group box 1 (HMGB1) is a crucial regulator of autophagy in response to cell stress.

In addition to its established role in the nucleus, HMGB1 has been shown to contribute to apoptosis and necrosis, so the authors tested whether HMGB1 is also involved in autophagy. First, they analysed the localization of HMGB1 in cultured cells in response to autophagic stimuli and found that HMGB1 translocated from the nucleus to the cytoplasm following both starvation and rapamycin treatment. This redistribution seemed to occur specifically in response to reactive oxygen species (ROS) generated downstream of autophagic stimuli.



HMGB1 regulates autophagy in mouse embryonic fibroblasts. Starvation promotes high mobility group box 1 (HMGB1; red) to translocate to the cytoplasm, where it colocalizes with Beclin 1 (green). In the absence of HMGB1, autophagy is not sustained, and Beclin 1 remains in complex with B cell lymphoma 2 (BCL-2; not shown). (nucleus, shown in blue). Image courtesy of Michael Lotze, University of Pittsburgh Cancer Institute, Pennsylvania, USA.

Tang *et al.* next observed that *Hmgb1*$^{-/-}$ mouse embryonic fibroblasts (MEFs) had fewer autophagic punctae than wild-type cells, and this could be restored by HMGB1 overexpression. The role of cytoplasmic HMGB1 in the autophagic process was assessed both by pharmacological inhibition of HMGB1 translocation from the nucleus and by the generation of cytoplasts (anucleate cells) that retain only cytoplasmic HMGB1. These experiments showed that the generation of autophagic punctae is greatly enhanced by the translocation of nuclear HMGB1, which suggests that HMGB1 translocation induces autophagy following prolonged cellular stress.

What then is HMGB1's mechanism of action? Following starvation stress, HMGB1 was found to interact with the autophagy protein Beclin 1 and to disrupt its interaction with B cell lymphoma 2 (BCL-2), which normally suppresses autophagy. This interaction was mediated by the disulphide-linked cysteine residues Cys23 and Cys45 of HMGB1, which promotes the dissociation of Beclin 1 from BCL-2. Furthermore, mutation of Cys106 promoted the cytoplasmic localization of HMGB1 and sustained autophagy. The authors conclude that oxidation of HMGB1 regulates its distribution and ability to facilitate autophagy, and present a model in which ROS generated by cellular stress promote HMGB1 translocation to the cytoplasm, which induces autophagy by disrupting the formation of a Beclin 1–BCL-2 complex.

This study has identified a new biological function for HMGB1 in promoting cell survival by sustaining autophagy in response to cellular stress, and has revealed a crucial new player in the ever-growing list of proteins that control autophagy. Relating these changes in autophagy to changes in metabolism represents the next hurdle.

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ORIGINAL RESEARCH PAPER Tang, D. *et al.* Endogenous HMGB1 regulates autophagy. *J. Cell. Biol.* **190**, 881–892 (2010)