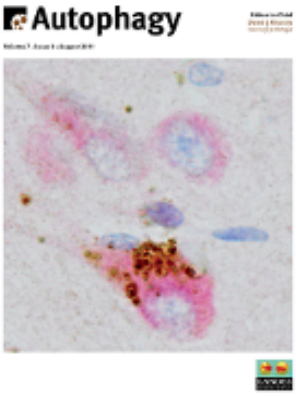

Autophagy
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/kaup20

Oncogene-induced autophagy and the Goldilocks principle

Seamus J. Martin

Published online: 01 Aug 2011.

To cite this article: Seamus J. Martin (2011) Oncogene-induced autophagy and the Goldilocks principle, Autophagy, 7:8, 922-923, DOI: 10.4161/auto.7.8.15821

To link to this article: http://dx.doi.org/10.4161/auto.7.8.15821

Autophagy 7:8, 922-923; August 2011; © 2011 Landes Bioscience

Oncogene-induced autophagy and the Goldilocks principle

Seamus J. Martin
Molecular Cell Biology Laboratory; The Smurfit Institute of Genetics; Trinity College; Dublin, Ireland

Although several oncogenes enhance autophagic flux, the molecular mechanism and consequences of oncogene-induced autophagy remain to be clarified. We have recently shown that expression of oncogenic H-Ras^{V12} promotes autophagy through upregulation of Beclin 1 and the BH3-only protein Noxa. H-Ras-expressing cells undergo autophagic cell death as a result of Noxa-mediated displacement of Mcl-1 and Bcl-x$_L$ from Beclin 1. Oncogenic H-Ras-induced death is attenuated through knockdown of *BECLIN 1*, *ATG5* or *ATG7*, or through overexpression of Mcl-1, Bcl-2, Bcl-x$_L$ and their close relatives. These observations suggest that high-intensity oncogene activation may be selected against by promoting excessive autophagy, leading to cell death. Consequently, such oncogenes may select for cells with a reduced capacity for autophagy, either through loss of a *BECLIN 1* allele or through upregulation of negative regulators of Beclin 1, such as Bcl-2 family members.

Key words: autophagic cell death, Beclin 1, Ras, Noxa, Mcl-1

Submitted: 04/05/11

Revised: 04/08/11

Accepted: 04/13/11

DOI: 10.4161/auto.7.8.15821

Correspondence to: Seamus J. Martin; Email: martinsj@tcd.ie

Punctum to: Elgendy M, Sheridan C, Brumatti G, Martin SJ. Oncogenic ras-induced expression of noxa and beclin-1 promotes autophagic cell death and limits clonogenic survival. Mol Cell 2011; 42:23–35; PMID: 21353614; DOI: 10.1016/j.molcel.2011.02.009.

Autophagy has a complex relationship with tumor development. On the one hand it seems that being able to mount effective autophagy-mediated recycling of cellular constituents may enable tumors to survive in the face of nutritional stress, ischemia, or due to organelle damage, as well as other stresses that tumors encounter more frequently than nontransformed cells. For example, Eileen White and colleagues have shown that impairment of autophagy, through knockdown of *BECLIN 1* or expression of constitutively activated Akt, greatly diminishes survival of transformed cells under ischemic conditions in vitro and in vivo. These considerations lead to the view that autophagy can be beneficial for tumors, increasing the adaptive capabilities of such cells and increasing their ability to survive the various challenges they encounter. This has led to the suggestion that autophagy inhibition may be a valid therapeutic strategy for treatment of certain cancers.

On the other hand, there is clear evidence that *BECLIN 1* is a haploinsufficient tumor suppressor gene; Beth Levine and others have shown that loss of a single *Beclin 1* allelle in the mouse greatly increases the rate of spontaneous tumor formation and also enhances the incidence of HPV-induced tumors. In addition, *BECLIN 1* is frequently mono-allelically deleted in human breast, ovarian and prostate cancer. Moreover, although cells doubly defective in autophagy and apoptosis survive ischemia less well in vitro, these cells paradoxically form tumors more rapidly in vivo. In this regard, the White laboratory has also found that compromised autophagy can lead to chromosomal instability, thereby acting as a driver of mutation leading to more aggressive tumors. These observations provide strong evidence that autophagy acts as a restraining influence on tumor development. Thus, in spite of the observations that autophagy may help tumors combat nutritional and ischemic stress, it would appear that autophagy can also be detrimental for such cells, and acts to oppose tumor establishment and progression.

The problem therefore is that there is evidence to argue that autophagy is both beneficial and detrimental to tumor development. However, both positions may be correct when we consider the Goldilocks principle. In the children's

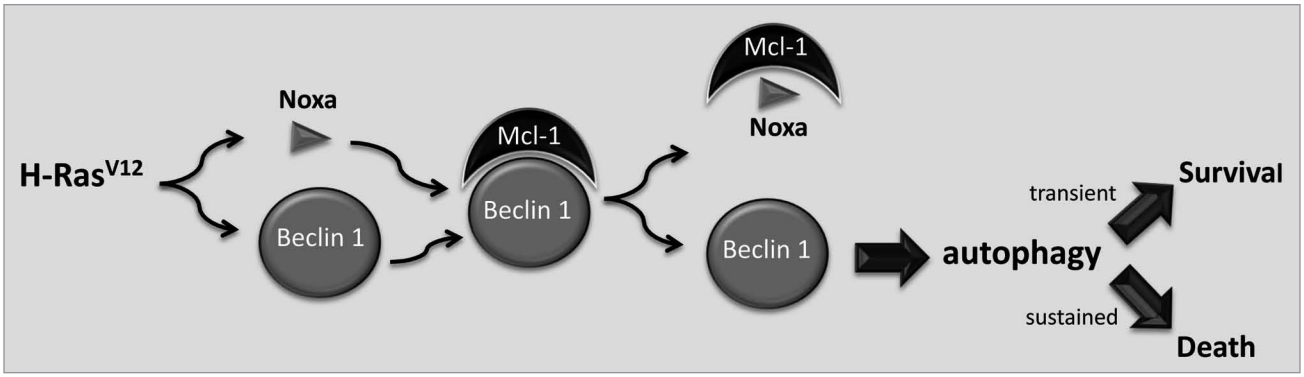

Figure 1. Oncogenic H-Ras^{V12} can promote autophagy through expression of Beclin 1 and the BH3-only protein, Noxa. Beclin 1-dependent autophagy can be inhibited through forming complexes with several members of the Bcl-2 family, such as Mcl-1, Bcl-x_L and Bcl-2 itself. Noxa can enhance H-Ras-induced autophagy through liberating Beclin 1 from Mcl-1. Sustained high-intensity oncogenic Ras activation can lead to autophagic cell death that can be attenuated through knockdown of *BECLIN 1*, *ATG5* or *ATG7*, or by overexpression of Bcl-2 family proteins such as Mcl-1 and Bcl-x_L.

tale, Goldilocks was the fussy child who only wanted things that fulfilled specific criteria; food could neither be too hot nor too cold, a bed could neither be too hard or soft, and so on. In other words, these needs had to fulfill specific tolerances, where there are limits on the plus and minus side of the desired objective. Tumor development may have a similar relationship with autophagy; the inability to mount an autophagic response may be bad (for the tumor) because this would prevent the tumor from raiding its own reserves when nutrients are in short supply—probably a frequent occurrence for cells disobeying normal growth controls. Highly proficient autophagy might also be unacceptable because, if carried to excess, it may successfully eradicate nascent tumors through cell death or completely prevent further mutations that permit tumor progression. Thus a tumor needs to get the autophagy balance right to avail of its advantages while avoiding the disadvantages of untrammeled or runaway autophagy. Therefore, from the tumor standpoint, the Goldilocks zone may be just sufficient autophagy to permit cells to survive ischemia and other stresses, while permitting some degree of buildup of damaged organelles; the latter can generate reactive oxygen species which can act as a driver of further mutations, leading to tumor progression.

Several recent studies, including one from our laboratory, have reported that deregulated Ras activity ramps up autophagy but with different outcomes, depending on the context. We found that oncogenic H-Ras can lead to increased autophagic flux that, if prolonged and not counteracted by cooperating oncogenes, leads to autophagic cell death within 5–7 days. H-Ras-induced autophagy is due to Ras-driven expression of Beclin 1 and the BH3-only protein Noxa (**Fig. 1**). The finding that Noxa is involved in this process was surprising given the link between this Bcl-2 family protein and apoptosis. However, in comparison with other members of the BH3-only protein family, Noxa is a poor inducer of apoptosis but is a good inhibitor of Mcl-1 and A1. Apart from its role as an inhibitor of apoptosis, Mcl-1 is also capable of binding to Beclin 1 and suppressing autophagy (**Fig. 1**). Indeed, we also found that H-Ras-induced autophagic cell death can be counteracted by overexpression of Mcl-1, A1 or Bcl-2, as well as other members of the pro-survival cohort of the Bcl-2 family, thereby restoring clonogenic survival in oncogenic H-Ras expressing cells.

Thus, high intensity H-Ras activation may drive aggressive autophagy that, if not strongly counterbalanced by other mutations to damp this down, might be incapable of driving tumor formation. Lower intensity Ras activation events may more naturally achieve a Goldilocks zone of beneficial autophagy and therefore become more readily positively selected without the need to counteract the increased autophagic flux. Setaluri and colleagues have also recently shown that high intensity expression of oncogenic B-Raf^{V600E} mutants fail to promote cell division and instead trigger autophagic cell death. Thus, too much or too little autophagy may be bad for tumors, providing a basis for the observation that *BECLIN 1* haplo-insufficiency, rather than loss of both *BECLIN 1* alleles, drives tumor formation.

Therefore, deregulated oncogenes need to stay within a given signaling threshold—yet another Goldilocks zone—of generating beneficial cell division and cell survival signals to avoid activation of tumor suppressive mechanisms such as cell cycle arrest, cell senescence, apoptosis or excessive autophagy. More aggressive oncogene activation events may be tolerated later on, when subsequent mutations have eroded these natural tumor suppressor mechanisms. Our recent study suggests that high intensity H-Ras signals are naturally self-limiting through induction of Beclin 1 and Noxa expression, which cooperate to promote excessive autophagy, culminating in cell death.

Acknowledgements

We thank Science Foundation Ireland (08/IN.1/B2031) and the European Union Marie Curie Research Training Network (ApopTrain) for support of the work discussed herein.