

Autophagy in Multiple Myeloma: What Makes You Stronger Can Also Kill You

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Autophagy, a process for recycling cellular constituents, is normally associated with cell survival and is thought to be beneficial for tumor maintenance. However, in this issue of *Cancer Cell*, Lamy and colleagues report that multiple myeloma utilizes caspase-10 to restrain autophagy and undergoes autophagic cell death upon its removal or inhibition.

Autophagy is a stress-induced catabolic process that is used to capture and eliminate defective organelles, protein aggregates, and intracellular microbes by targeting these to lysosomes for destruction (reviewed in Choi et al., 2013). Autophagy can also be deployed to recycle bulk cytoplasmic constituents in response to starvation, thereby sustaining cell survival. The role of autophagy in tumorigenesis has been debated. There is evidence supporting the view that autophagy is ramped up in transformed cells and is beneficial for tumor maintenance and progression (reviewed in White, 2012). On the other hand, there is also evidence to argue that excessive autophagy can act as a tumor-suppressive mechanism (Elgendy et al., 2011; Choi et al., 2013), possibly through initiation of cell death or senescence. Autophagic cell death typically displays none of the features of apoptosis and can be attenuated through ablation of key autophagy regulators such as Atg proteins or Beclin-1. There has been skepticism that cells can die through excessive autophagy (Kroemer and Levine, 2008), however, a significant body of evidence is emerging to argue that autophagic cell death occurs in several important contexts (Das et al., 2012). In this issue of *Cancer Cell*, Lamy et al. (2013) provide support for the idea that deregulated autophagy can result in cellular autodestruction in multiple myeloma.

Multiple myeloma is a clonal B cell malignancy arising from plasma cells, which are specialized antibody-producing cells critical for antibody-based immunity. Upon activation by the appropriate antigen, B cells differentiate into long-lived plasma cells that are equipped with

an extensive endoplasmic reticulum (ER) and serve as antibody factories, synthesizing prodigious quantities of immunoglobulin. However, the latter capability is a source of proteotoxic stress due to misfolding of a proportion of newly synthesized immunoglobulin, the accumulation of which can lead to ER stress and cell death if not properly dealt with. Plasma cells solve this problem by ramping up several protein handling systems, including the ubiquitin-proteasome pathway, the unfolded protein response (UPR) pathway, and the autophagy machinery. Autophagy facilitates the removal of protein aggregates by encapsulating these in autophagosomes, followed by their degradation through fusion with lysosomes. Indeed, a recent study has shown that mice deficient in a critical component of the autophagy machinery, Atg5, preferentially lose Atg5-deficient plasma cells and are compromised in making long-term antibody responses as a result (Pengo et al., 2013). Thus, plasma cells rely heavily on autophagy, as well as other protein degradation systems, to keep the factory floor free of debris that would otherwise choke up the antibody production line. Because of this, multiple myeloma displays particular sensitivity to proteasome inhibitors, such as bortezomib, and the possibility of combining such treatments with inhibitors of autophagy is under investigation (Aronson and Davies, 2012).

Using an RNA interference library screening approach, Lamy et al. (2013) searched for molecules critical for the survival of multiple myeloma cells. Somewhat counter-intuitively, caspase-10, a protease normally associated with induction of apoptosis in response to TNF

family members, emerged as a survival factor for all myeloma cell lines tested (Lamy et al., 2013). This observation was confirmed using a variety of approaches. Further investigation revealed that inhibition of caspase-10 or knockdown of a molecule involved in facilitating its activation, cFLIP_L, led to a dramatic increase in autophagic flux followed by cell death lacking features of apoptosis. More compellingly, knockdown of two constituents of the autophagy machinery, Atg5 or Beclin-1, led to protection from cell death caused by caspase-10 inhibition (Lamy et al., 2013). Taken together, these data suggest that caspase-10 sets a threshold for autophagy in multiple myeloma that, if breached, can lead to autophagic cell death (Figure 1).

So how does caspase-10 put the brakes on autophagy? Lamy et al. (2013) found that BCLAF1, a protein of uncertain function that was originally identified as a binding partner of pro-survival Bcl-2 family members, might be the key target of caspase-10 in this context (Figure 1A). Although members of the Bcl-2 family are well known for their role as inhibitors of apoptosis, several members of this family also directly interact with and inhibit Beclin-1, thereby suppressing autophagy (Elgendy et al., 2011; Choi et al., 2013). Silencing of BCLAF1 expression in myeloma abrogated cell death caused by caspase-10 inhibition, whereas overexpression of BCLAF1 promoted cell death with features of autophagy. Thus, upon inhibition of caspase-10, BCLAF1 is stabilized and displaces Bcl-2 from Beclin-1 thereby ramping up autophagy and leading to cell death (Figure 1B). Several questions remain to be resolved, however. The precise nature

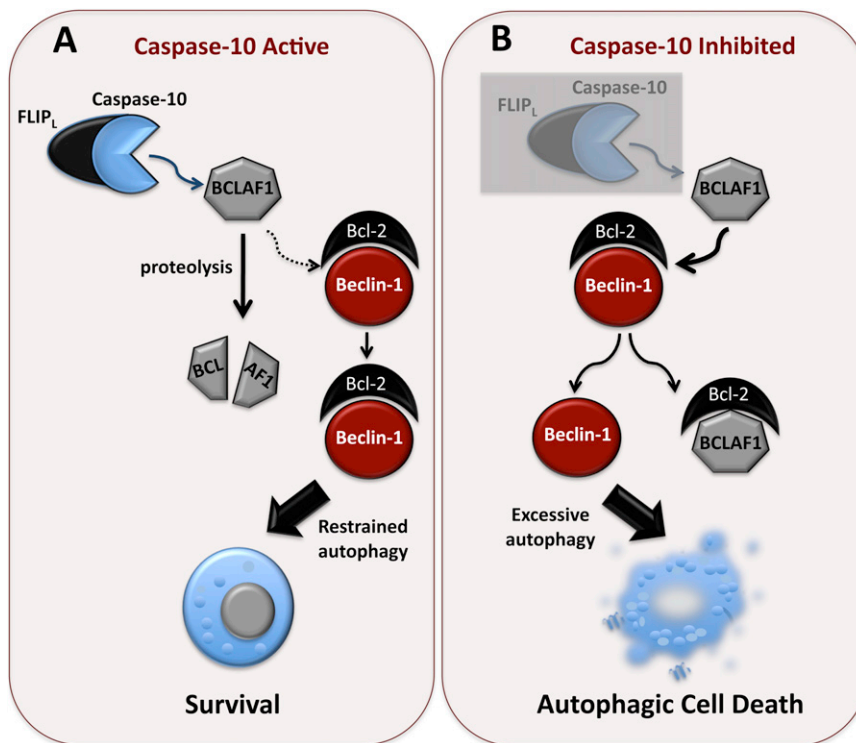


Figure 1. Caspase-10 Puts a Brake on Autophagy in Multiple Myeloma
(A) Under steady-state conditions in multiple myeloma, a FLIP_L/caspase-10 complex cleaves and inactivates BCLAF1 preventing its participation in autophagy.
(B) Upon inhibition or knockdown of caspase-10, BCLAF1 becomes stabilized, displacing Bcl-2 from Beclin-1, leading to excessive autophagy followed by autophagic cell death.

of the FLIP_L/caspase-10-activating complex remains to be clarified, as does the issue of whether assembly of this complex is spontaneous or driven by autocrine or paracrine death receptor signals. The role of BCLAF1 as a driver of autophagy and how deregulated autophagy leads to cell death also require significant clarification.

Interestingly, previous studies have also implicated autophagy as a component of the cell death response of multiple myeloma to inhibitors of the protein handling machinery. Inhibition of autophagy partly antagonized the cytotoxic effects of bortezomib, suggesting that autophagic cell death may be partly responsible for the cytotoxic effects of proteasome inhibitors in myeloma (Hoang et al., 2009). Silencing of the UPR sensors PERK, IRE1, or ATF6 also led to the death of myeloma cells via excessive induction of autophagy (Michallet et al., 2011). Thus, due to the pressures resulting from the accumulation of misfolded immunoglobulin, multiple myeloma may

be uniquely predisposed toward autophagic cell death if protein handling pathways are tampered with.

One implication of the current study is that the process leading to the transformation of plasma cells places their malignant counterparts in a precarious state of “autophagic stress” that needs to be reined in for such cells to survive. Indeed, this may be a general property of many tumors, as several oncogenes such as H-Ras, B-Raf, and Myc have been found to ramp up autophagy by different mechanisms. Thus, excessive autophagy may represent a tumor suppressor mechanism that needs to be counteracted during tumorigenesis to constrain this tendency toward self-immolation. Varying solutions to this problem are likely to be found among different tumors, with some losing one allele of the Beclin-1 gene, as is frequently seen in breast, prostate, and ovarian tumors, while others upregulate the expression of Bcl-2 family proteins that can inhibit the actions of Beclin-1 (Choi et al., 2013). Multiple alternative

strategies may also be employed to constrain autophagy within acceptable limits, such as the caspase-10-dependent mechanism described by Lamy et al. (2013).

Thus, autophagy appears to be a double-edged sword that can be beneficial as well as detrimental to tumor development. Tumors need to get the autophagy balance right to avail its advantages, which help to cope with the demands of limited nutrient and oxygen supply, while avoiding the disadvantages of untrammelled autophagy, which can lead to excessive self-consumption of cellular resources.

An obvious therapeutic implication of the finding that caspase-10 acts as a survival factor in multiple myeloma is that inhibitors of caspase-10 might have therapeutic utility in this malignancy. However, such inhibitors would have to be sufficiently specific to avoid disruption of caspases in critical processes such as apoptosis and inflammation. One of the key lessons from the current study is that, in cancer, too much autophagy may be as bad as too little. Thus, encouraging the self-cannibalistic tendencies of multiple myeloma may be a viable therapeutic strategy.

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