

## Autophagy joins the game to regulate NF- $\kappa$ B signaling pathways

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The nuclear factor kappa B (NF- $\kappa$ B) transcription factor coordinates several aspects of innate and adaptive immunity, inflammation, cell survival and proliferation [1, 2]. Dysregulation of the NF- $\kappa$ B pathway has been associated with cancer development and progression as well as with other human diseases including viral infections and a number of inflammatory diseases [1]. NF- $\kappa$ B is formed through the dimerization of 5 subunits, including members of the Rel protein family, namely RelA (p65), c-Rel, RelB, NF- $\kappa$ B1 (p50 and its precursor p105) and NF- $\kappa$ B2 (p52 and its precursor p100). Two pathways are involved in the activation of NF- $\kappa$ B. In both these pathways, kinase activity and proteasome activity play a major role in freeing NF- $\kappa$ B from cytoplasmic inhibitors to promote its nuclear translocation and activation. The classical or canonical pathway is activated by a large range of stimuli (microbial and viral infections, proinflammatory cytokines). In this pathway, NF- $\kappa$ B dimers, mostly p50/RelA and p50/c-Rel, are usually retained in the cytoplasm by their interaction with specific inhibitors, called I $\kappa$ Bs. Stimuli activate NF- $\kappa$ B through I $\kappa$ B kinase (IKK)-dependent phosphorylation (the IKK complex is composed of 2 kinase subunits, IKK $\alpha$  and IKK $\beta$  and a nonenzymatic regulatory subunit, IKK $\gamma$ ) and subsequent proteasomal degradation of I $\kappa$ B proteins. The alternative or non-canonical pathway, triggered by a limited number of stimuli, plays a central role in the generation of lymphoid organs and in B-cell maturation and survival. In this pathway, NF- $\kappa$ B dimers p52/RelB or p52/p52 are activated by the limited proteasomal degradation of the NF- $\kappa$ B2/p100 precursor. This proteolysis is initiated by the activation of IKK $\alpha$  homodimers by upstream NF- $\kappa$ B-inducing kinase (NIK). Unlike mature IKK proteins, which are stable, the mature NIK is rapidly degraded by the proteasome in a TRAF3-dependent manner. In a report published in

a recent issue of *Cell Research*, Xiao and co-workers [3] report that NIK is a novel “client” for the multichaperone heat shock protein (Hsp90) via an interaction involving its C-terminal part. Surprisingly, the main role of Hsp90 is not to help folding of newly synthesized NIK but to suppress its degradation by macroautophagy. Macroautophagy (called here autophagy) is a bulk catabolic pathway for cytoplasmic components (macromolecules and organelles) initiated by the formation of a vacuole called an autophagosome that ultimately fuses with lysosomes where the sequestered material is degraded [4]. Inhibition of Hsp90 function by geldanamycin (GA) leads to the autophagic degradation of NIK and inhibition of p100 processing. Thus the maturation and activity of NIK is regulated by both autophagy and the proteasome. Whether Hsp90 is involved in NIK regulation by TRAF3 and whether Hsp90 plays a role in the survival function of NF- $\kappa$ B are questions that remain to be elucidated. Recent studies by the same group have shown that IKK proteins, which are clients of Hsp90, are also substrates for the autophagic pathway when freed by GA treatment [5]. Overall, these findings provide the first evidence that client proteins of Hsp90 are not degraded exclusively by the proteasome system [6]. However, as shown by Xiao and colleagues [3], the protein kinase Akt/PKB, another Hsp90 client, is not a substrate for autophagy, suggesting that some selectivity exists regarding the propensity of Hsp90 client proteins to be degraded by autophagy. The selectivity of autophagic sequestration towards proteins has also been reported in other settings [7]. Determination of the basis for this selectivity is a major challenge and would contribute to a better understanding the role of autophagy in regulating cell functions. As many Hsp90 clients are associated with oncogenesis and cell survival [6], it would be interesting to define the repertoire of client proteins that

are sensitive to autophagy because of the importance of this process in tumor progression and the control of cell survival [4]. Another unanswered general question concerns the effect of GA on autophagy. In other words, are NIK and IKK selectively targeted to the autophagic pathway that proceeds at a basal rate or does GA stimulate autophagy? This latter possibility would suggest that some autophagic regulators are clients of Hsp90.

The work by Xiao and colleagues [3] also impacts on the crosstalk between NF- $\kappa$ B and autophagy during tumor progression. NF- $\kappa$ B activation has been shown to control the expression of cell-cycle genes, apoptosis inhibitors and proteases that promote the invasive phenotype [2]. On the other hand, there is now mounting evidence that autophagy may suppress tumor growth [4]. This suppressor function is probably linked to different roles of autophagy, such as initiating cell death, protecting DNA from genotoxic stresses and limiting inflammation. The autophagic degradation of IKK and NIK would limit the role of NF- $\kappa$ B in cancer development through its function in cell survival, angiogenesis, invasiveness and inflammation. It is worth noting that not only autophagy regulates NF- $\kappa$ B activity but reciprocally autophagy is regulated by NF- $\kappa$ B. In fact, recent studies have shown that Tumor Necrosis factor (TNF) $\alpha$ -induced NF- $\kappa$ B activation represses autophagy [8]. When NF- $\kappa$ B is inhibited, TNF $\alpha$  triggers autophagy, which contributes to the TNF $\alpha$ -induced apoptotic signal. The mechanism by which NF- $\kappa$ B represses autophagy remains to be determined but it may involve activation of mTOR (mammalian Target of Rapamycin) [8], a kinase that plays an important role in the signaling control of autophagy [9], and regulation of the expression of other regulators of autophagy [8].

Most chemotherapeutic agents and even  $\gamma$  irradiation activate NF- $\kappa$ B [10]. The promising clinical development of a GA derivative [6] would offer a new adjuvant to conventional anti-cancer treatment to help overcome NF- $\kappa$ B-

dependent chemoresistance. However, because of the role of NF- $\kappa$ B in immune responses, there may be limitations to long-term treatment by NF- $\kappa$ B inhibitors due to the possibility of patients developing immunodeficiency [2]. The discovery that NF- $\kappa$ B signaling pathways are regulated by autophagy offers a way of bypassing the resistance of cancer cells to anticancer treatments [8]. However, before this can happen, ways must be found of using the accumulating knowledge on autophagy to develop effective anticancer therapies [4].

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