Editorial

Targeting Inhibitor of Apoptosis Proteins to Block Vascular Inflammation

Le Anh Luong, Paul C. Evans

The tumor necrosis factor (TNF) receptor superfamily (TNFRSF) represents a large number of membrane-bound and secreted proteins that regulate inflammation and other functions in the vasculature and other tissues. Members of the TNFRSF are involved in the pathogenesis of atherosclerosis, and treatment with anti-TNFα antibodies enhances vascular function in patients with arthritis. Activation of TNFRSF members triggers multiple intracellular signaling pathways that influence diverse cellular activities. This complexity is exemplified by TNF receptor 1 (TNFR1), the founder member of the TNFRSF, where signaling activates dual nuclear factor-κB (NF-κB) and p38/c-Jun-N-terminal kinase mitogen-activated protein kinase (MAPK) pathways that cooperate to induce and stabilize proinflammatory transcripts. Signaling through TNFR1 also drives an NF-κB-independent proapoptotic signaling pathway. However, this pathway is suppressed in endothelial cells by a parallel NF-κB-dependent survival pathway, which involves transcriptional activation of cytoprotective genes.

Thus, a deeper understanding of the factors that regulate TNFR signaling may inform the development of novel therapies that suppress TNFR-dependent inflammatory activation while retaining the prosurvival activities of this receptor. This concept was brought into sharp relief by Mayer et al7 in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, who demonstrated that targeting cellular inhibitor of apoptosis proteins (cIAPs) can block inflammatory activation of endothelial cells without sensitizing them to apoptosis. The authors initially used animal models to demonstrate that pretreatment with small peptides that destabilize cIAPs can suppress inflammation, in part by reducing leukocyte recruitment to vascular endothelial cells. Subsequent studies of cultured endothelial cells revealed that inhibitor of apoptosis protein (IAP) inhibitors blocked activation of c-Jun-N-terminal kinase and p38 and suppressed the induction of inflammatory molecules by TNF-α. However, NF-κB activation and cell viability were not influenced by IAP inhibition. Thus, it is plausible that targeting of IAPs reduces inflammatory activation while preserving cell viability by uncoupling cytoprotective NF-κB activity from inflammatory MAPK signaling (Figure). This hypothesis should now be addressed further, eg, by testing whether NF-κB can activate antiapoptotic genes in the presence of IAP inhibitors.

Mayer et al then investigated the function of IAPs in the MAPK and NF-κB pathways by examining the effects of IAP inhibitors on the activity of various TNFR signaling intermediaries. The regulation of TNFR signaling has been studied intensely (Figure). Briefly, activation of TNFR1 leads to the recruitment of numerous signaling intermediaries (including TNFR1-associated death domain protein, TNFR-associated factor 2, receptor-interacting protein 1 [RIP1], NF-κB essential modulator, and cIAPs) to its cytoplasmic tail. These proteins in turn control the activation of TGFβ-activated kinase 1 (TAK1), an MAPK kinase kinase that acts upstream from cascades of kinase activities. Thus, TAK1 activates MAPK kinases, which, in turn, activate p38 and c-Jun-N-terminal kinase by phosphorylation. TAK1 also phosphorylates IKB kinase-2, which subsequently induces nuclear localization and transcriptional activation of NF-κB by promoting ubiquitination and proteosomal degradation of inhibitor of κB molecules. Studies over the past decade have revealed that NF-κB and MAPK signaling relies on modification of RIPI, TAK1, and other components of the TNFR1 complex with noncanonical forms of polyubiquitin. These chains act as platforms for the recruitment of TAK1 (via TAK1-binding proteins) and IKB kinase (via NF-κB essential modulator) to promote TAK1-dependent activation of IKB kinase. IAPs and TNFR-associated factor proteins play a central role in this process, as they function as ubiquitin ligases to catalyze ubiquitination of TNFR intermediaries. Intriguingly, TNFR signaling generates several different structural forms of polyubiquitin, which may have specific roles in regulating downstream signaling pathways.11 Mayer et al found that IAP inhibitors modulate these signaling processes by inhibiting TNFR-associated factor 2 expression and by suppressing (but not entirely abolishing) RIP1 ubiquitination and TAK1 phosphorylation. Thus, it is plausible that cIAP inhibitors block TAK1–MAPK kinase–p38/c-Jun-N-terminal kinase signaling by modulating IAP- or TNFR-associated factor 2-mediated ubiquitination of RIP1 (Figure).

Intriguingly, IAP inhibitors had no effect on NF-κB activation in endothelial cells even though they reduced RIP1 ubiquitination and TAK1 phosphorylation. One possibility is that attenuated RIP1-TAK1 signaling was insufficient for MAPK activation but above a critical threshold required for NF-κB activity. A more elegant scenario is that IAP inhibitors may block specific polyubiquitin modifications that drive
MAPK signaling, while allowing the generation of other forms of polyubiquitination that signal to NF-κB. It is noteworthy that although the inhibitors used in this study almost completely ablated cIAP1 expression, they had relatively modest effects on cIAP2. It is therefore plausible that IAP inhibitors uncouple downstream signaling by blocking cIAP1-dependent MAPK activation, without impeding cIAP2-driven NF-κB activity. Additional basic biology studies of the specific functions of cIAP1 and cIAP2 in endothelial cells are required to test these ideas further.

In summary, the findings of Mayer et al. provide important clues to the functions of cIAP proteins in endothelial cells and suggest that IAP inhibitors can dampen inflammation without the undesirable effects associated with cytotoxicity. The potential ability of IAP inhibitors to prevent or treat atherosclerosis; their influence on plaque components, including smooth muscle cells and macrophages; and their ability to modulate signaling downstream from other TNFRSF members should now be studied.

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References

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