Inflammation and cell death are two essential, dichotomic elements in the response to pathogenic organisms or tissue injury, critical for initiating an immune response and preventing establishment of a replicative niche for intracellular pathogens. However, if unregulated, both can cause or contribute to disease conditions, particularly those caused by autoinflammation. Therefore, understanding how they are controlled is critical for the development of new therapeutics. Transforming growth factor 1 activating kinase (TAK1) is an apical kinase governing activation of both of these pathways. It is pivotal in regulating activation of Receptor-interacting protein (RIP) kinase I following stimulation of TNFR1, as inhibition or loss of TAK1 initiates RIP1-mediated apoptosis or RIP1–RIP3-mediated necrosis (Guo et al., 2016). When present, TAK1 is considered an important component of proinflammatory signaling through activation of NF-κB downstream of TNFR1 or TLR receptor activation, where it acts downstream of ubiquitinated RIP1 or TRAF6, respectively (Mihaly et al., 2014). Given its central role in these fundamental inflammatory pathways, TAK1 inhibitors have attracted significant attention as potential therapeutics for triggering cell death in cancer therapy or limiting inflammatory signaling in autoimmune disorders (Sakurai, 2012). Paradoxically, when tested in animal models, these inhibitors have caused autoinflammatory disorders, though the mechanism through which this occurs was not understood.

In this issue, Malireddi and colleagues used a myeloid-specific TAK1 KO mouse to shed new light on a novel, antiinflammatory function of TAK1 in macrophages that may explain, at first sight, the paradoxical inflammatory findings. As previously demonstrated in other cell models, they found that TAK1 deletion or inhibition resulted in spontaneous death of the TAK1-deficient macrophages, mediated by enhanced RIP1 and RIP3 signaling (Malireddi et al., 2018). Strikingly, however, these cells also underwent spontaneous NLRP3 inflammasome activation in the absence of any exogenous signals. This was surprising, as inflammasome activation is heavily regulated because of their high inflammatory potential. This is particularly true for NLRP3, which requires a minimum of two signals for activation: a priming signal that increases transcription of NLRP3, followed by a second stimulus that activates NLRP3, triggering assembly of the inflammasome, release of proinflammatory cytokines, including IL-1β, and pyroptosis, a caspase-1-dependent form of inflammatory cell death (Pröchnicki et al., 2016). It is therefore particularly remarkable that TAK1 deficiency removes the requirements for both an exogenous priming signal, occurring through RIP1-mediated unregulated TNFα secretion, and the second activating signal through deregulation of TNFR1 signaling, enabling NLRP3 activation (see figure). This posits TAK1 as an essential regulator of NLRP3 activation in macrophages, contrasting to the initial hypothesis of TAK1 as a proinflammatory molecule.

It is interesting to note that in spite of ongoing NLRP3-driven inflammation, the TAK1 myeloid-deficient mice were not reported to display signs of autoinflammatory diseases, but rather loss of myeloid cells and an increase in neutrophils. This was...
TAK1 restrains both NLRP3 priming and activation. TAK1 activity restricts NLRP3 priming by limiting spontaneous activation of RIP1, preventing activation of NF-κB and subsequent release of TNFα. It then restrains TNFα/TNFRI-driven NLRP3 activation through an unknown mechanism.

Overall, this study consolidates TAK1 inhibitors as attractive targets for therapeutics in cancer therapy, as it is central to multiple cell death pathways. The involvement of NLRP3-driven inflammation adds extra impetus to such a treatment, as it has been shown that NLRP3 activation in various tissue environments can activate an NK cell response, which could contribute to clearance of the tumor (Dagenais and Saleh, 2016; van den Boorn et al., 2016). Thus, the dual function of a TAK1 inhibitor to cause cancer cell death while simultaneously activating NLRP3 makes it a potentially powerful anticancer agent, albeit with the provision that such a drug would have to be properly dosed to avoid undesired autoinflammatory responses and prevent depletion of the myeloid compartment. These results also suggest that TAK1 might be a poor target for antiinflammatory therapies, as its inhibition, at least in macrophages, would drive rather than inhibit inflammation.