Chemotherapy engages multiple pathways leading to IL-1β production by myeloid leukocytes

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Interleukin-1β (IL-1β) can limit tumor growth by promoting T cell-mediated antitumor immune responses. Several chemotherapeutic agents can stimulate the production of IL-1β by tumor-infiltrating leukocytes via the NLRP3 inflammasome. We have recently demonstrated that some chemotherapeutics can also trigger the secretion of IL-1β by driving the assembly of the caspase-8- and FADD-containing platform known as the ripoptosome.

Innate immunological signals delivered by tumor-resident dendritic cells (DCs) and macrophages (MΦ) can contribute to the efficacy of chemotherapeutic agents by engaging T cell-mediated adaptive immune responses that limit the expansion of chemotherapy-resistant tumor cells.1 Interleukin-1β (IL-1β) has emerged as a particularly relevant MΦ/DC-derived cytokine that—depending on tumor type and microenvironmental features—can either inhibit tumor growth by T cell-dependent mechanisms or support tumor progression. The latter activity of IL-1β may involve1 the release of paracrine growth factors from stromal cells of the tumor environment;2 enhanced tumor angiogenesis; and/or3 the accumulation of myeloid-derived suppressor cells (MDSC), which suppress antitumor immnosurveillance (reviewed in Refs.1,2). Given such contrasting roles for IL-1β in tumor growth and anticancer therapy, it is important to define the signaling pathways that underlie the production of IL-1β by MΦs and DCs in the context of diverse antitumor chemotherapeutic regimens.

Previous studies have identified 2 distinct, but not mutually exclusive, molecular cascades that lead to the secretion of IL-1β (Fig. 1). The aim of most chemotherapeutic agents is to directly promote apoptosis or necrosis among rapidly dividing neoplastic cells, which generally results in the accumulation of tumor-derived macromolecules (e.g., high mobility group box 1, HMGB1) and small metabolites (e.g., ATP) in the tumor microenvironment. These molecules act as danger-associated molecular patterns (DAMPs) and engage the canonical cascade involving the assembly of a multiprotein caspase-1-activating platform that includes NLR family, pyrin domain containing 3 (NLRP3) as well as the PYD and CARD domain containing adapter (PYCARD), best known as ASC. This complex, commonly known as the NLRP3 inflammasome, promotes the secretion of bioactive IL-1β from tumor-resident MΦs and DCs. Although this pathway also involves a direct activity of chemotherapy on MΦs and DCs, it is independent of the classical NLRP3 inflammasome but rather reflects the engagement of a signaling cascade involving receptor-interacting protein kinase 1 (RIPK1) and resulting in the assembly of a Fas (TNFRSF6)-associated via death domain protein (FADD)- and caspase-8-containing supramolecular complex known as the ripoptosome (Fig. 1). These findings add to a growing literature on the important role for caspase-8 as both an alternative

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IL-1β-converting enzyme and a regulator of canonical inflammasomes. Notably, the ripoptosome-dependent production of IL-1β was triggered by some common chemotherapeutic agents (e.g., doxorubicin, staurosporine) but not by others (e.g., oxaliplatin, cisplatin). The ability of the various drugs to activate caspase-8 in myeloid cells and hence drive IL-1β secretion correlated with their efficacy to inhibit the expression of members of the inhibitor of apoptosis protein (IAP) family. The release of DIABLO (an IAP-binding protein best known as Smac) from mitochondria suppresses the E3 ubiquitin ligase activity of IAPs, hence inhibiting the ubiquitin-dependent degradation of ripoptosomes. The downregulation of baculoviral IAP repeat containing 2 (BIRC2, a member of the IAP family also known as cIAP1) in doxorubicin-treated DCs appeared to be critical for the preservation of the FADD/caspase-8 ripoptosome, corroborating previous results that implicated the downregulation of IAPs in the processing of IL-1β as triggered by Smac mimetics.

The identification of a caspase-8-dependent pathway for IL-1β production has several implications in the context of anticancer chemotherapy. First, Toll-like receptor 4 (TLR4) signaling in the tumor-resident MΦs or DCs of cancer patients undergoing chemotherapy may be activated by commensal bacteria-derived endotoxins that leak across compromised gut epithelial barriers or by tumor-derived DAMPs, such as HMGB1. Such an activation of TLR4 may synergize with chemotherapy agents, such as doxorubicin, to
trigger the FADD/caspase-8 ripoptosome in vivo. Second, in contrast to caspase-1 (which is predominantly expressed in myeloid cells), caspase-8 is ubiquitously expressed. The caspase-8-dependent processing of IL-1β may thus occur in non-myeloid stromal compartments of the tumor microenvironment, including epithelial cells, endothelial cells and fibroblasts, as well as in some neoplastic cells, which do not express high levels of caspase-1 but may express pro-IL-1β in particular inflammatory contexts.

Ongoing studies indicate that the ability of particular chemotherapeutic agents to drive the caspase-8-dependent processing of IL-1β correlates with their ability to elicit pro-apoptotic signaling cascades in MΦs or DCs, even in the context of the NF-κB signals that are required for production of pro-IL-1β. This is likely to be relevant given the prominent role of NF-κB in transactivation of anti-apoptotic/pro-survival genes. Malignant cells proliferate rapidly in comparison to MΦs and DCs, and most chemotherapeutic agents act on cancer cells by inducing molecular injuries (e.g., DNA damage) that activate networks resulting in the transcriptional or post-transcriptional activation of pro-apoptotic proteins (e.g., pro-apoptotic Bcl-2 family members). A key issue is therefore to discriminate how a particular drug may differently integrate NF-κB-driven pro-inflammatory vs. anti-apoptotic gene expression in malignant cells vs. tumor-resident immune cells. Moreover, given the key role of organelar dysfunction in the activation of NLR3 inflammasomes and ripoptosomes, the analysis of the effects of chemotherapeutic agents on mitochondrial, lysosomal, and plasma membrane integrity will likely provide novel insights into the multiple pathways underlying IL-1β production in different tumor models.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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