

Inflammasome-independent IL-1 β release by myeloid cells in the tumor microenvironment promotes immune suppression and therapy resistance

Background: One of the central pro-inflammatory cytokines, IL-1 β , is produced as inactive pro-IL-1 β that requires proteolytic processing. The canonical pathway of pro-IL-1 β processing observed during infections, tissue damage and autoinflammation involves the activation of inflammasomes, multiprotein complexes that detect danger signals via intracellular receptors, such as NLRP3, and trigger the activation of caspase-1 which cleaves pro-IL-1 β into bioactive IL-1 β . Caspase-1 also triggers a lytic form of cell death required for IL-1 β release called pyroptosis via proteolytic activation of gasdermin D. There is emerging evidence to support that IL-1 β has a detrimental impact on tumor progression. However, the signaling pathway controlling IL-1 β release in tumors and the effect of the cytokine on the tumor microenvironment have not been fully elucidated.

Methods: Using flow cytometry and histological analyses, we evaluated tumor characteristics in mouse Lewis lung carcinoma and E0771 breast carcinoma models in IL1b^{-/-} mice. We used Nlrp3^{-/-}, Casp1/11^{-/-} and Gsdmd^{-/-} mice to investigate the involvement of the canonical IL-1 β -processing and release pathway in controlling IL-1 β -driven inflammation in tumors.

Results: We found that IL-1 β expression was limited to myeloid cells, including monocytes, macrophages, dendritic cells and neutrophils in both human and mouse breast and lung carcinomas. IL-1 β -deficiency abrogated the tumor-induced systemic mobilization and recruitment of immunosuppressive neutrophils which resulted in increased abundance of tumor-infiltrating effector T cells and inhibited tumor progression both in murine lung and breast carcinomas. Although IL-1 β deletion alone did not affect tumor angiogenesis, we found that tumors resistant to anti-angiogenic anti-VEGFR2 therapy were rendered sensitive in IL-1 β -deficient hosts. Interestingly, secretion of bioactive IL-1 β by tumor-associated myeloid cells and consequential neutrophil recruitment was independent of the canonical NLRP3/caspase-1/gasdermin D-mediated IL-1 β processing and release pathway both in lung and breast carcinomas.

Conclusions: Our study demonstrates that IL-1 β suppresses antitumor immunity and contributes to therapy resistance, providing a rationale for IL-1 β neutralization strategies in cancer. However, our results suggest that inhibition of inflammasomes or pyroptosis will likely not be beneficial due to inflammasome-independent IL-1 β release by tumor-associated myeloid cells.

Keywords : IL-1, inflammasome, neutrophil, angiogenesis, pyroptosis

Authors :

References : , , ,

Authors

Máté Kiss 1, Lieselotte Vande Walle 2, Els Lebegge 1, Helena Van Damme 1, Aleksandar Murgaski 1, Evangelia Bolli 1, Jiri Keirsse 1, Yvon Elkrim 1, Maria Solange Martins 1, Amelie Fossoul 2, Manuel Ehling 3, Samantha Pretto 3, Jens Serneels 3, Junbin Qian 4, Diether Lambrechts 4, Massimiliano Mazzone 3, Andy Wullaert 5, Mohamed Lamkanfi 2, Jo Van Ginderachter 1, Danya Laoui 1,

1. Myeloid Cell Immunology Lab, VIB Center for Inflammation Research, Brussels, BELGIUM

2. NOD-like Receptor and Inflammasome Laboratory, VIB Center for Inflammation Research, Ghent, BELGIUM

3. Laboratory of Tumor Inflammation and Angiogenesis, VIB Center for Cancer Biology, Leuven, BELGIUM

4. Laboratory for Translational Genetics, VIB Center for Cancer Biology, Leuven, BELGIUM

5. Intestinal Host-Microbe Communication Laboratory, VIB Center for Inflammation Research, Ghent, BELGIUM