Inhibition of the inflammasome AIM2 in human lung cancer-derived immunesuppressive Plasmacytoid Dendritic cells as a novel pharmacological target

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Plasmacytoid dendritic cells (pDCs) highly populate tumor masses and are strictly correlated to bad prognosis. However, their role in cancer is still controversial. Therefore, to understand their activity in human lung cancer, we isolated pDCs from human samples of lung obtained from non-small cell lung cancer (NSCLC) patients. Human lung tumor masses presented higher percentage of pDCs ($B220^{+}CD19^{-}BDCA\text{-}2^{+}CD123^{+}$cells) than healthy tissues and they were in their immunesuppressive phenotype as determined by higher levels of CD33 and PD-L1. In addition, although HLA-A and HLA-D higher expression, cancerous pDCs were not able to exert cytotoxic activity against tumor cells but instead promoted their proliferation. In this scenario, cancerous pDCs were able to produce high levels of type I IFN and IL-1α after the activation of the inflammasome absent in melanoma 2 (AIM2), but not Nod-like receptor NLRP3. The release of IL-1α was significantly reduced by the blockade of type I IFN receptor and of AIM2 via the addition of LL-37. Importantly, mitochondrial-derived reactive oxygen species (mtROS) sequesters diminished AIM2-dependent IL-1α release.
Our data demonstrate that the immunesuppressive lung tumor-associated pDCs release IL-1α via AIM2 inflammasome, which activation is type I IFN- and mtROS-dependent. Therefore, strategies aiming at modulating AIM2 activity in tumor-associated pDCs might prove to limit tumor cell proliferation in the lung.