The ecto-ATPDase CD39 is involved in the acquisition of the immunoregulatory phenotype by M-CSF-macrophages and ovarian cancer tumor-associated macrophages: Regulatory role of IL-27

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Tumor-associated macrophages (TAM) are immunosuppressive cells that can massively accumulate in the tumor microenvironment. In patients with ovarian cancer, their density is correlated with poor prognosis. Targeting mediators that control the generation or the differentiation of immunoregulatory macrophages represents a therapeutic challenge to overcome tumor-associated immunosuppression. The ectonucleotidase CD39 hydrolyzes ATP into extracellular adenosine that exhibits potent immunosuppressive properties when signaling through the A2A adenosine receptor. We report here that CD14(+) CD163(+) TAM isolated from ovarian cancer patients and macrophages generated in vitro with M-CSF, express high levels of the membrane ectonucleotidase CD39 compared to classically activated macrophages. The CD39 inhibitor POM-1 and adenosine deaminase (ADA) diminished some of the immunosuppressive functions of CD14(high) CD163(high) CD39(high) macrophages, such as IL-10 secretion. We identified the cytokine IL-27, secreted by tumor-infiltrating neutrophils, located close to infiltrating CD163(+) macrophages, as a major rheostat of CD39 expression and consequently, on the acquisition of immunoregulatory properties by macrophages. Accordingly, the depletion of IL-27 downregulated CD39 and PD-L1 expression as well as IL-10 secretion by M-CSF-macrophages. Collectively, these data suggest that CD39, driven by IL-27 and CD115 ligands in ovarian cancer, maintains the immunosuppressive phenotype of TAM. This work brings new information on the acquisition of immunosuppressive properties by tumor-infiltrating macrophages.

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