Role of extracellular ATP and its receptor P2X7 in anti-tumoral immune response

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Extracellular ATP (eATP) recently emerged as a major constituent of tumor microenvironment modulating cell growth and migration but also tumor host–interactions, including vessel formation and immune-cancer cell cross talk. Amongst purinergic receptors, P2X7 is probably the best-recognized regulator of tumor cell proliferation, movement and matrix invasion (Adinolfi et al. 2015a). On the other hand, P2X7 is also known to mediate immune cell activation and secretion of pro-inflammatory cytokines such as IL-1β. In an attempt to evaluate the role of P2X7 in tumor-host interaction, we analyzed cancer growth in P2X7 wild type and null mice. In a first set of experiments, we induced either melanoma or colon carcinoma formation in two different mice strains (C57Black/6, Balbc/J) expressing or not P2X7 (Adinolfi et al. 2015b). In both experimental settings, the absence of P2X7 receptor in the host caused increased tumor growth if compared to the wild type control. Moreover, lack of P2X7 favored melanoma spreading to the lungs. These differences could be, at list partially, ascribable to reduced immune infiltration. In fact, the presence of lymphocytes and macrophages/dendritic cells retrieved at tumor-host interface was greatly reduced in P2X7 null mice versus wild type controls (Adinolfi et al. 2015b). Due to its ability of causing the opening of a pore permeable to large solutes the P2X7 receptor was implicated in eATP secretion. This prompted us to evaluate whether the absence of P2X7 receptor could also influence eATP levels during oncogenesis. To address this issue we took advantage of a luciferase derived-probe engineered to be expressed at the outer facet of the plasma membrane (PmeLUC) allowing for *in vivo* eATP measure (Pellegatti et al. 2008). We obtained WEHI-3B mouse leukemia cells stably expressing the PmeLuc probe that emits photons in an ATP dependent fashion, and injected these cells in either wild type of P2X7 null syngeneic mice. Thanks to the use of a total body mice luminometer, we were able to follow eATP variations in live animals during tumor progression. Interestingly, the development of increased size tumors in P2X7 null mice was accompanied by reduced eATP in the tumor milieu suggesting that the nucleotide could play a role in the recruitment of immune cells. Conversely, systemic, administration of P2X7 antagonists caused a decrease in tumor growth that was in turn accompanied by reduced levels of eATP. Taken together our data suggest that P2X7 receptor expressed by either cancer or host cells differentially modulates eATP levels in the tumor microenvironment affecting immune cell infiltration.

Adinolfi et al. (2015) *Current Medicinal Chemistry*. 22(7):878-90.
Adinolfi et al. (2015) *Cancer Research*. 75(4):635-44.
Pellegatti et al. (2008) *PLoS One*. 3(7):e2599.