

Mast cells are directly activated by cancer cells by a mechanism involving autocrine formation of adenosine and autocrine/paracrine signaling of the adenosine A3 receptor.

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Mast cells (MCs) constitute an important part of the tumor microenvironment (TME). However, the underlying mechanisms of their activation within the TME remain poorly understood. Here we show that recapitulating cell-to-cell contact interactions by exposing MCs to membranes derived from a number of cancer cell types, results in MC activation, evident by the increased phosphorylation of the ERK1/2 MAP kinases and Akt, in a phosphatidylinositol 3-kinase dependent fashion. MC activation by cancer cells results in the upregulation and release of interleukin 8 as well as release of microRNA containing exosomes. Cell contact mediated activation of the MCs is phenocopied by cancer cell derived extracellular vesicles. Strikingly, cancer cell mediated activation of MCs by cell-to-cell contact or extracellular vesicles involves autocrine formation of adenosine and is mediated by the adenosine A3 receptor. Collectively, our findings provide evidence for a novel mode of crosstalk between MCs and cancer cells implicating direct activation by cancer cells in MC reprogramming into a pro tumorigenic profile.