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Innate immune cells promote gastric tumorigenesis

Moritz Eissmann[1], Ernst M[1], Masson F[1], Buchert M[1], O' Donoghue R[1], Phesse T[1], Dijkstra C[1], Jarnicki A[2] and **Grimbaldeston M[3]**
[1]Olivia Newton-John Cancer Research Institute, Australia
[2]University of Newcastle, Australia
[3]Centre for Cancer Biology, Australia

Innate immune cells can either promote or inhibit tumor growth. Among the different types of innate cells, the function of mast cells (MC) in gastric cancer (GC) is not well understood. Here we study the role of MC and macrophages (MΦ) in tumor initiation and maintenance in mouse models for GC. Furthermore, we explore the anti-tumorigenic potential of targeting MC/MΦ using small molecule inhibitors. MC density was highly elevated in the sub-mucosa of gastric tumors in gp130FF-mice, in a gp130-wild type murine GC model, as well as in human GC. Genetic depletion of MC in gp130FF; cKitWsh/Wsh-mice and MC inhibition, *via* cromolyn administration, decreased tumor burden in gp130FF-mice. Both, MC-deficiency and pharmacological MC-inhibition were associated with decreased angiogenesis and proliferation, increased hypoxia and a reduction in tumor-associated macrophages density. Accordingly, MΦ-depletion, *via* clodronate treatment of gp130FF-mice led to a significant reduction of tumor burden again associated with reduced tumor angiogenesis and proliferation. Furthermore, simultaneous therapeutic MC/MΦ-targeting completely blocked gastric tumor growth in gp130FF-mice. Mechanistically, we show that IL33 is highly expressed in gp130FF tumors and that gastric MC expresses the IL33 receptor, St2. Moreover, IL33-stimulation of MC isolated from gastric tumors of gp130FF-mice increased expression and secretion of the MΦ -attracting chemokines Ccl2, Ccl3 and Ccl7. Tumor-associated MC promote tumor growth and angiogenesis in inflammation-associated gastric cancer by recruitment of MΦ by mechanisms likely to include IL-33. Since individual or combined pharmacological targeting of MC/MΦ impedes gastric tumor growth, these cells may therefore represent novel therapeutic targets for inflammation-associated GC.

moritz.eissmann@onjcri.org.au

Morphine modulates interleukin-4 or breast cancer cell induced prometastatic activation of macrophages

Samira Khabbazi[1], Marie-Odile Parat[1] and **Yannick Goumon[2,3]**
[1]University of Queensland, Australia
[2]Centre National de la Recherche Scientifique, France
[3]University of Strasbourg, France

Interactions between cancer cells and stromal cells in the tumor microenvironment play a key role in the control of invasiveness, metastasis and angiogenesis. Macrophages display a range of activation states in specific pathological contexts and alternatively activated (M2) macrophages can promote tumor aggressiveness. Opioids are able to modulate tumor growth and metastasis. We tested whether morphine modulates the activation of macrophages induced by interleukin-4 (IL-4), the prototypical M2 polarization inducing cytokine or co-culture with breast cancer cells. We showed that IL-4 causes increased MMP-9 production and expression of the alternative activation markers arginase-1 and MRC-1. Morphine prevented IL-4-induced increase in MMP-9 in a naloxone and methyl naltrexone reversible fashion. Morphine also prevented IL-4-elicited alternative activation of RAW264.7 macrophages. Expression of MMP-9 and arginase-1 were increased when RAW264.7 was subjected to paracrine activation by 4T1 cells and this effect was prevented by morphine *via* an opioid receptor mediated mechanism. Morphine further decreased 4T1 breast cancer cell invasion elicited by co-culture with RAW264.7. Reduction of MMP-9 expression and alternative activation of macrophages by morphine was confirmed using mouse bone marrow derived macrophages. Taken together, our results indicate that morphine may modulate tumor aggressiveness by regulating macrophage protease production and M2 polarization within the tumor microenvironment.

s.khabbazi@uq.edu.au