

## INNATE IMMUNITY, INFLAMMATION AND CANCER: FROM BENCH TO BEDSIDE

Alberto Mantovani, MD

Istituto Clinico Humanitas, Humanitas University, Via Manzoni 113, Milan, Italy and William Harvey Research Institute, London, UK.

Innate immunity consists of a cellular and a humoral arm. Tumor-associated macrophages are a key component of tumor-promoting inflammation. The long pentraxin PTX3 as originally cloned (cDNA and genomics, mouse and human) as an IL-1 inducible gene. We have used the long pentraxin PTX3 as a paradigm for the humoral arm of innate immunity and its interplay with cells. Components of humoral innate immunity including PTX3 and Complement are a key component of the tumor microenvironment. Moreover, the evidence on the role of complement in macrophage recruitment and functional skewing of macrophages will be discussed. In addition we recently discovered that IL-1R8, which we cloned as TIR8 and also identified as SIGIRR, serves as a checkpoint restraining NK cell mediated resistance against carcinogenesis and metastasis. In the same vein, we originally identified a tetraspan-like molecule (MS4A4A) in polarized M2 and M2-like macrophages. The function of this molecule and its role in the interplay with NK cells in resistance to metastasis will be discussed. Thus macrophages engage in a complex interaction with innate lymphoid cells which plays a key role in tumor immunity.

### References

- Mattiola I, Tomay F, De Pizzol M, Silva-Gomes R, Savino B, Gulic T, Doni A, Lonardi S, Boutet MA, Nerviani A, Carriero R, Molgora M, Stravalaci M, Morone D, Shalova IN, Lee Y, Biswas SK, Mantovani G, Sironi M, Pitzalis C, Vermi W, Bottazzi B, Mantovani A, Locati M. The interplay of the macrophage tetraspan MS4A4A with Dectin-1 and its role in NK cell-mediated resistance to metastasis. *Nature Immunol*, Jul 1. doi: 10.1038/s41590-019-0417-y. [Epub ahead of print].
- Ponzetta A, Carriero R, Carnevale S, Barbagallo ML, Molgora M, Perucchini C, Magrini E, Gianni F, Kunderfranco P, Polentarutti N, Pasqualini F, Di Marco S, Supino D, Peano C, Cananzi F, Colombo P, Pilotti S, Alomar SY, Bonavita E, Galdiero MR, Garlanda C, Mantovani A, Jaillon S. Neutrophils driving unconventional T cells mediate resistance against murine sarcomas and selected human tumors. *Cell*, 178(2):346-360, 2019.
- Molgora M, Bonavita E, Ponzetta A, Riva F, Barbagallo M, Jaillon S, Popovic B, Bernardini G, Magrini E, Gianni F, Zelenay S, Jonjic S, Santoni A, Garlanda C, Mantovani A. IL-1R8 is a checkpoint in NK cells regulating anti-tumor and anti-viral activity. *Nature*, 551:110-114, 2017.
- Bonavita E, Gentile S, Rubino M, Maina V, Papait R, Kunderfranco P, Greco C, Feruglio F, Molgora M, Laface I, Tartari S, Doni A, Pasqualini F, Barbati E, Basso G, Galdiero MR, Nebuloni M, Roncalli M, Colombo PG, Laghi L, Lambris JD, Jaillon S, Garlanda C, Mantovani A. PTX3 is an extrinsic oncosuppressor regulating complement-dependent inflammation in cancer. *Cell* 160: 700-714, 2015.
- Mantovani A., Marchesi F., Laghi L., Malesci A., Allavena P. Tumor-associated macrophages as treatment targets in oncology. *Nature Rev, Clin. Oncol.* 14(7):399-416, 2017.