HUMANITAS UNIVERSITY

EXPERIMENTAL IMMUNOPATHOLOGY

PROJECT 1

Project title
"Exploring the role of neutrophils and unconventional T cells in antitumor immunity"

Pre-clinical: Sebastien Jaillon, Sebastien.jaillon@hunimed.eu
Laboratory name: Experimental Immunopathology

Abstract
Cancer-related inflammation, including the presence of inflammatory leukocytes in the tumor microenvironment (TME) is recognised as a hallmark of cancer. Therefore, exploration of the immune contexture of the TME is crucial for the development of new therapeutic approaches, as demonstrated with the immune checkpoints.
Neutrophils are present in the TME but their role in cancer is poorly understood.
In preclinical models, our current studies revealed the essential role played by neutrophils in resistance against primary carcinogenesis by driving the polarisation of a new population of unconventional T cells (UTCs) endowed with antitumor properties.
Using a multitask approach, combining state-of-the-art technologies with the advantage of genetically engineered mice, models of primary carcinogenesis and investigation in human samples, our project aims to dissect cellular and molecular mechanisms involved in the neutrophil-UTC antitumor axis, defining its potential activity in immunotherapy.

Main technical approaches
- Animal handling (Murine models of carcinogenesis)
- Blood and tissues sampling from mice
- Cellular Biology (purification and culture of cells from blood and tissues, culture of cell lines)
- Flow cytometry
- Molecular Biology (PCR, Real-time PCR, RNAsequencing)

Scientific references
1) IL-1R8 is a checkpoint in NK cells regulating anti-tumor and anti-viral activity.
Molgora M, Bonavita E, Ponzetta A, Riva F, Barbagallo M, Jaillon S, Popović B, Bernardini G, Magrini E, Gianni F, Zelenay S, Jonjić S, Santoni S, Garlanda C, Mantovani A. Nature. 2017. Nov 2;551(7678):110-114.

2) Occurrence and significance of tumor-associated neutrophils in patients with colorectal cancer.
Galdiero MR, Bianchi P, Grizzi F, Di Caro G, Basso G, Ponzetta A, Bonavita E, Barbagallo M, Tartari S, Polentarutti N, Malesci A, Marone G, Roncalli M, Laghi L, Garlanda C, Mantovani A, Jaillon S. Int J Cancer. 2016 Jul 15;139(2):446-56.

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3) PTX3 is an extrinsic oncosuppressor regulating complement-dependent inflammation in cancer

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 M.R, Nebuloni M, Roncalli M, Colombo, P., Laghi, L., Lambris J.D, Jaillon S, Garlanda C, Mantovani A. Cell. 2015. Feb; 160(4):700-14.

4) Neutrophils in the activation and regulation of innate and adaptive immunity.

Mantovani A, Cassatella MA, Costantini C, Jaillon S. Nat Rev Immunol. 2011 Jul 25;11(8):519-31.

5) CCR7 is involved in the migration of neutrophils to lymph nodes.

Beauvillain C, Cunin P, Doni A, Scotet M, Jaillon S, Loiry ML, Magistrelli G, Masternak K, Chevailler A, Delneste Y, Jeannin P. Blood. 2011 Jan 27;117(4):1196-204.

6) The humoral pattern recognition receptor PTX3 is stored in neutrophil granules and localizes in extracellular traps.

Jaillon S, Peri G, Delneste Y, Frémaux I, Doni A, Moalli F, Garlanda C, Romani L, Gascan H, Bellocchio S, Bozza S, Cassatella MA, Jeannin P, Mantovani A. J Exp Med. 2007 Apr 16;204(4):793-804.

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PROJECT 2

Project title
"Development of a novel checkpoint molecule of lymphoid cells in cancer"

Pre-clinical: Cecilia Garlanda, cecilia.garlanda@hunimed.eu
Laboratory name: Experimental Immunopathology

Abstract
IL-1R8 is a member of the IL-1 receptor family with negative regulatory functions. Recently it has been observed that in Natural Killer cells IL-1R8 acts as a checkpoint and that its genetic deletion increases the maturation and functional activities of NK cells towards tumors, metastases and viral infections. The aim of the project is to extend the knowledge on the role of IL-1R8 in the functional activity of lymphocytes and to develop the inhibition of this molecule as a therapeutic target in preclinical cancer models.
The student will be involved in preclinical cancer and metastasis studies. In parallel, she/he will develop in vitro models of functional activation of lymphocytes using different IL-1R8 inhibition and / or silencing approaches in these cells. He will then be involved in the study of the relevance in human of the data collected in the animal by studying the expression of IL-1R8 in human samples and through in silico bioinformatics approaches.

Main technical approaches
Techniques used include in vivo models of cancer and immunotherapy; leukocyte purification and functional assays; FACS analysis; ELISA; molecular biology; microscopy.

Scientific references
1- Garlanda C, Dinarello CA, Mantovani A. The interleukin-1 family: back to the future. Immunity. 2013 Dec 12;39(6):1003-18.

2- Molgora M, Barajon I, Mantovani A, Garlanda C. Regulatory Role of IL-1R8 in Immunity and Disease. Front Immunol. 2016 Apr 20;7:149. doi: 10.3389/fimmu.2016.00149. eCollection 2016.

3- 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 P, Laghi L, Lambris JD, Jaillon S, Garlanda C*, Mantovani A*. PTX3 is an extrinsic oncosuppressor regulating complement-dependent inflammation in cancer.
Cell. 2015 Feb 12;160(4):700-14. doi: 10.1016/j.cell.2015.01.004.*Cocorresponding authors.

4- Campesato LF, Silva APM, Cordeiro L, Correa BR, Navarro FCP, Zanin RF, Marçola M, Inoue LT, Duarte ML, Molgora M, Pasqualini F, Massara M, Galante P, Barroso-Sousa R, Polentarutti N, Riva F, Costa ET, Mantovani A, Garlanda C, Camargo AA. High IL-1R8

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expression in breast tumors promotes tumor growth and contributes to impaired antitumor immunity. Oncotarget. 2017 Jul 25;8(30):49470-49483. doi: 10.18632/oncotarget.17713.
5- Molgora M, Bonavita E, Ponzetta A, Riva F, Barbagallo M, Jaillon S, Popović B, Bernardini G, Magrini E, Gianni F, Zelenay S, Jonjić S, Santoni A, Garlanda C, Mantovani A. IL-1R8 is a checkpoint in NK cells regulating anti-tumour and anti-viral activity. Nature. 2017 Nov 2;551(7678):110-114. doi: 10.1038/nature24293.

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