# **ImmunoTools** *special* Award 2014

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## Immunomodulatory properties of CSC on human peripheral monocytes.

Cancer stem cells (CSCs), for their resistance to chemotherapic agents and their tumor initiating ability may play a relevant role in the pathogenesis and prognosis of tumors. Renal CSC have been described by Camussi et collaborators as a population of tumor-initiating cells by means of cell sorting with a mesenchymal marker CD105. The $CD105^{+}$ renal CSCs expressed other mesenchymal stem cell markers such as CD44, CD90, CD146, CD73, CD29, and vimentin; embryonic stem cells markers such as Nanog, Oct4 and Nestin. Recent data indicate that CSCs interact with tumor microenvironment by a two-directional release of factors to promote CSC maintenance on one side, and to induce tumor growth, through their interactions with the tumor microenvironment. Besides soluble factors, exosomes/microvesicles released from tumor cells have recently emerged as potential candidates that can support tumor angiogenesis, vasculogenesis, growth, and the formation of pre-metastatic niches.

Solid tumors have been known to be strongly infiltrated by inflammatory leukocytes, and in various mouse and human malignancies a strict correlation between increased numbers of macrophages and poor prognosis has been demonstrated. Based on this, both the recruitment and activation of tumor-associated macrophages (TAMs) are regarded as pivotal to tumor progression, and TAMs are considered putative targets for therapeutic intervention. TAMs originate as blood monocytes recruited from the tumor vasculature by tumor-derived signals, such as M-CSF, MCP-1, VEGF and Angiopoietin-2. Recruitment of monocytes is one of the primary events in tumor development. Cytokines and hypoxia have the capacity to pilot recruitment, maturation and differentiation of infiltrating leukocytes. The phenotype of TAMs is strongly

influenced by tumor microenvironment which appears to promote their protumoral functions.

Macrophages have numerous functions related to tissue remodeling, inflammation, immunity and thrombosis and have the capacity to affect tumor growth and progression. In analogy with the Th1 and Th2 dichotomy, macrophages can be phenotypically polarized by the microenvironment to mount specific M1 or M2 functional programs. M1 macrophage activation in response to microbial products or interferon- are characterized by the production of copious amounts of pro-inflammatory cytokines, high capacity to present antigen and consequent activation of a polarized type I response. In contrast, various signals (e.g. IL-4, IL-13, glucorticoids, IL-10) induce distinct M2 functions, able to dumpen inflammatory responses and induce adaptive Th2 immunity, scavenge debris, promote angiogenesis and tissue remodeling. One of the most important characteristics of TAMs include their ability to directly affect tumor growth through promotion of angiogenesis, as well as the survival and metastasis of tumor cells. Immunosuppressive cytokines IL-10 and TGF are produced by many tumors. IL-10 promotes an M2 pathway of macrophage activation and induces TAMs to express M2-related functions. The production of IL-10, TGF and PGE2 by cancer cells and TAMs contributes to a general suppression of antitumor activities. TAMs have poor antigen presenting capacity and can suppress T cell activation and proliferation. Moreover, TAMs are able to induce T regulatory cells (Treg).

Targeting macrophages may present a potential strategy to control tumor growth. However, understanding the signaling pathways involved in the ‘switch’ of macrophage polarization states (i.e. M1 to M2) in the early stages of tumor progression may help to develop new therapies aimed at preventing this and re-orientating M2 TAMs in favour of a more anti-tumoral phenotype. The aim of this project is to study the possible interactions between renal CSC and peripheral blood-derived monocytes. In particular we are interested to know if CSC can affect monocyte to macrophages differentiation. Preliminary experiments indicate that CSC can directly interact with monocytes and that the result of this interaction is different in the presence of cell-to-cell contact or not.

ImmunoTools reagents will be very helpful in performing co-culture experiments of CSC and monocytes as well as immunophenotypic and functional analysis of differentiating macrophages.

**ImmunoTools** *special* AWARD for **Laura Chiossone** includes 21 reagents

FITC - conjugated anti-human CD3, CD14, CD16, CD33, CD45, Annexin V,

PE - conjugated anti-human CD1a, CD11b, CD14, CD34, CD43, CD80, HLA-ABC, HLA-DR,

recombinant human cytokines: rh EGF, rh GM-CSF, rh IFNgamma, rh IL-4, rh M-CSF, rh TNFα, rh VEGF-A/VEGF-165 DETAILS more AWARDS