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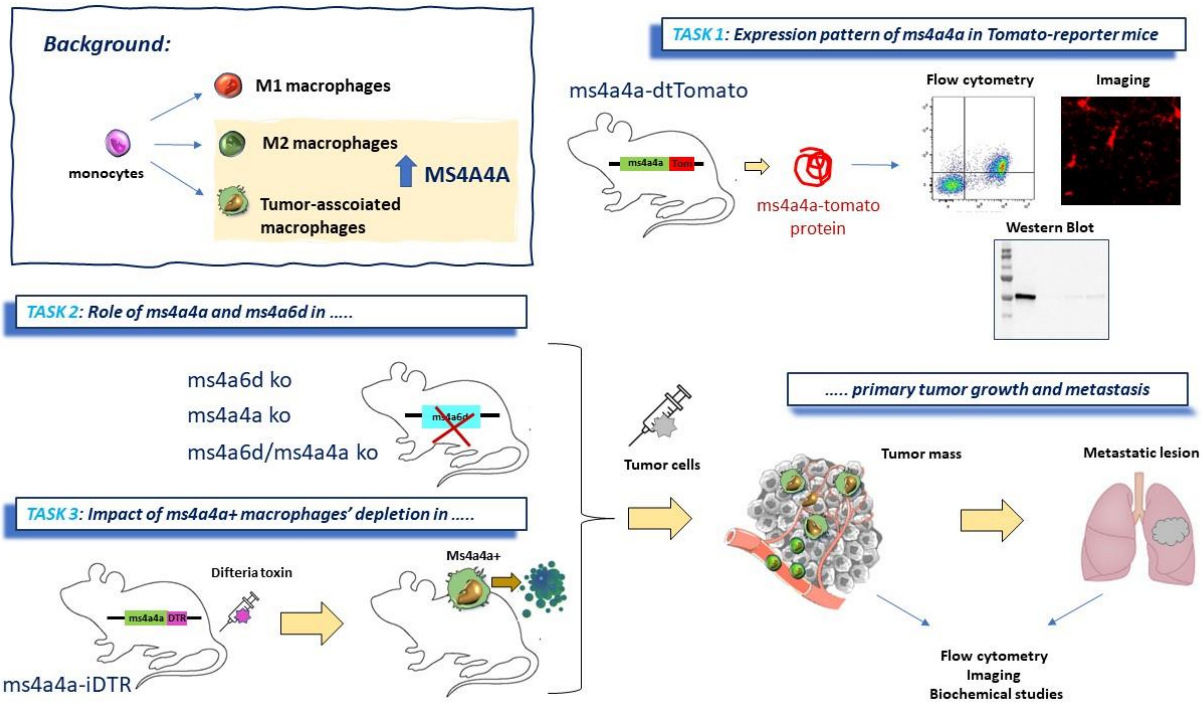
Identification of novel strategies targeting macrophages in immune response to tumors

Macrophages are cells of the innate immune system, they play an important role in the inflammatory response by removing pathogens and cellular debris by phagocytosis and by producing various soluble mediators. Furthermore, they are the main tumor-infiltrating host cells. Experimental mouse models have shown that tumor-associated macrophages (TAMs) are a critical element in tumor growth and progression and in metastasis processes, both by supporting tumor growth and regulating the specific immune response against the tumor. In recent years, several clinical studies have clearly associated high TAM levels with poor prognosis for the patient.

The MS4A protein family is composed of 18 members expressed on myelomonocytic cells, dendritic cells, and lymphoid cells under physiological or pathological conditions. Most of MS4A proteins have no known function: mostly perform their biological function by influencing the membrane positioning of other molecules with which they associate; others have been found to be involved in the control of tumor growth, acting directly on tumor cells or indirectly as they are expressed by tumor infiltrating immune cells.MS4A4A and MS4A6D are the two tetraspanins studied in this project. MS4A4A has been identified by our lab and another group, with restricted expression on human and murine M2-type macrophages and tumor-associated macrophages. Recent evidence showed that MS4A4A expressed by macrophages regulates metastatic spread in some tumors, through the engagement of Dectin-1 and activation by NK cells. Furthermore, recent publication reported expression of ms4a6d, the mouse homolog of MS4A6D, in murine macrophages. Ms4a6d interacts with V-set and immunoglobulin 4 (Vsig4) domain, acting as a membrane adapter for the recruitment of JAK2, intervenes in the regulation of intracellular STAT3/A20 signaling mediated by inhibiting the activation of NF-κB and the consequent transcriptional repression of Nlrp3 and Il1b. This suggests that Ms4a6d plays a role in the negative regulation of the macrophage inflammatory profile.

Given the lack of information in the literature on the role of ms4a6d expressed by macrophages in a tumor context and the possible interaction with ms4a4a in membrane microdomains, this project aims to evaluate the role of the tetraspanins ms4a4a and ms4a6d expressed by TAM in the tumor microenvironment. The function of TAMs in the local growth and metastatic spread of two transplantable tumor cell lines will then be defined, by using mouse models that carry the combined depletion of the two proteins of interest ms4a4a and ms4a6d and by conditional depletion of macrophages expressing ms4a4a.



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