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Titolo	ROLE OF CCL2 AND ITS RECEPTORS CCR2 AND D6 IN THE ACTIVATION AND POLARIZATION OF TUMOR-ASSOCIATED MACROPHAGES [Tesi di dottorato]
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Sommario	Chemokines are well known to play a major role in tumor progression and metastasis. In particular CCL2 is over-expressed in several human cancers and their higher levels correlate with poor prognosis and shorter outcomes. Here we reported two different studies in which CCL2 receptors, the canonical CCR2 and the atypical D6 (or ACKR2) were examined for their involvement in tumor progression. In particular D6 was investigated for its expression and its ability to shape CCL2 gradient in Kaposi's sarcoma, whereas CCR2 has been analyzed as potential modeler of TAM polarization. D6 is an atypical chemokine receptor acting as a decoy and scavenger for inflammatory CC chemokines expressed in lymphatic endothelial cells. Here, we report that D6 is also expressed by Kaposi's sarcoma (KS) which is a tumor ontogenetically related to lymphatic endothelium, yet its role in tumor progression was hitherto unknown. D6 expression was evaluated by immunohistochemistry in a cohort of KS patients and its role in cancer progression was investigated in an in vivo KS model. Both in human tumors and in the experimental model, D6 expression levels were inversely correlated with tumor aggressiveness, and directly correlated with increased chemokine-driven infiltration of macrophages and their acquisition of a pro-angiogenic phenotype. Inhibition of monocyte recruitment reduced growth of D6-incompetent tumors, while adoptive transfer of wt but

	not CCR2-/- macrophages increased the growth rate of D6-competent neoplasms. In the KS model, which presents the B-Raf V600E activating mutation, inhibition of B-Raf or downstream ERK pathway induced D6 expression, and in progressing human KS tumors activation of the K-Ras/B-Raf/ERK pathway correlate with reduced levels of D6 expression. These results indicate that activation of the K-Ras/B-Raf/ERK pathway during KS progression down-regulates D6 expression, which unleashes chemokine-mediated macrophage recruitment and their acquisition of an M2-like phenotype supporting angiogenesis and tumor growth. Thereafter, we wanted to deeper investigate how CCR2 support TAM M2 polarization firstly by using an in vitro system. Wt and CCR2-/- macrophages were polarized with M1 and M2 stimuli and analyzed for gene expression and cytokines production. While no difference was found in M2 polarized macrophages, CCR2-/- M1 or LPS activated macrophages showed higher expression of inflammatory genes and reduced production of the anti-inflammatory cytokine IL-10 and of the pro-angiogenic cytokine VEGF when compared to wt macrophages. The impaired IL-10 production was also confirmed by treating human monocytes with the CCR2 antagonist RS-504393. After LPS stimulation, CCR2-/- macrophages showed reduced activation of NF-kB and p38 MAPK when compared to wt macrophages indicating a cross talk between CCR2 and TLR4 signaling pathways. The contribution of CCR2 to cancer growth was evaluated with a transplantable lung cancer model that grew slower when co-injected with CCR2-/- macrophages, presenting a marked M1 phenotype of infiltrating TAM and a higher number of both CD4+ and CD8+ T cells, correlated with a decreased number of splenic T regulatory cells when compared to wt macrophages holding-tumors. Taken together these data indicate that CCR2 expression by macrophages not only induce their recruitment to tumor site but also affect their polarization and anti-tumor potential.
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