

CCR5+ REGULATORY T CELLS INDUCED BY METASTATIC BREAST CARCINOMAS MIGRATE TOWARD A GRADIENT OF CCL8 AND ACCUMULATE IN THE PRIMARY TUMOUR AND METASTATIC LUNG TISSUE

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Despite their role in the regulation of immunity toward innocuous antigens, regulatory T cells (Tregs) may contribute to tumour growth and metastasis by suppressing T cell-mediated anti-tumor cytotoxicity. Expression of CCR5 by CD4⁺CD25⁺Foxp3⁺ Tregs is important for their intratumoral migration and immune-suppressive function. Disruption of CCR5 signalling through antagonism of the CCR5 receptor or its ligands has been found to decrease the growth and metastasis of melanoma, pancreatic and colon cancers in pre-clinical immunocompetent models. The objectives of this study are to determine if CCR5⁺ Tregs are recruited to primary breast tumours and metastatic sites, and to examine their role in the development of metastatic foci. We have found that the metastatic mammary carcinomas 4T1 and 4T07 induce the accumulation of CCR5⁺ Tregs in the primary tumour and metastatic lungs of mice. CCR5⁻ Tregs were observed in non-metastatic 67NR primary tumours, although Tregs were not elevated in the lungs of 67NR tumour-bearing mice. The production of CCL8, an endogenous ligand of CCR5, was increased in the primary tumour and lungs of 4T1 and 4T07 tumour-bearing mice, and our preliminary data suggest that CCL8 may be secreted by macrophages *in vivo*. Tregs migrated toward CCL8 *ex vivo*, and this migration was inhibited by the CCR5 antagonist, Maraviroc, without impacting Treg viability. We are currently investigating whether treatment of tumour-bearing mice with Maraviroc decreases the accumulation of CCR5⁺ Tregs *in vivo* and the formation of lung nodules in mice bearing metastatic mammary carcinomas. The inhibition of CCR5 represents a viable therapeutic strategy to prevent Treg homing to sites of tumour growth without systemically depleting them, thereby avoiding the off-target effects of global Treg depletion such as autoimmunity. Ultimately, we hope to advance the development of targeted, immune-based therapeutics for the treatment of metastatic breast cancer.