



# CCR5 inhibition in colorectal cancer patients

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Immunotherapy in metastatic colorectal cancer is a challenge. I would like to thank Dr. Mukaida for his comprehensive commentary (1) on our work (2). A couple of points were raised that I will address in this letter. Immunotherapy with new immune checkpoint inhibitors is a different approach (3) compared to the immunotherapies based on vaccination or cytokine application. While for vaccination approaches no clear benefit was identified in colorectal cancer (4), combined chemotherapy with cytokines (GOLFIG trial) showed clinical effects, albeit at the price of autoimmune side effects (5). This situation highlights the complexities of immunotherapies quite well and shows that patients with microsatellite-unstable colorectal cancer are a limited subgroup within colorectal cancer (6). The rate of MSI positive colorectal cancer liver metastases is excessively low. In our own analyses, no positive liver metastasis was found. Within the MARACON trial also no tumor was MSI positive. So immunotherapy, even the newest checkpoint inhibitors, have to cope with difficult terrain in metastatic colorectal cancer. Our work as well as the work of others has shown that colorectal cancer primary tumors become CCR5 positive only in advanced stages (7), only with metastatic spread to lymph nodes or distant organs. This begs of course the question, whether the CCR5 expression is directly related to invasive tumor cell behavior (8) or whether this is just an epiphenomenon. Currently available data from other cancer entities (9) suggests that it is indeed a signature of invasive behavior and the question whether one could block distant metastasis in localized colorectal cancer by using CCR5 inhibitors as adjuvant is completely unclear. The role of the CCL5/CCR5 axis in cancer is diverse (10). For colorectal cancer we can say that a genetic variation (the famous *CCR5*del32

mutation), which leads to a loss of the extracellular receptor domain and therefore to a defect in CCR5 signaling is associated with a delayed but not abrogated occurrence of distant metastasis in colorectal cancer patients (unpublished data). This strongly suggests that CCL5/CCR5 is only a part in the complex network of metastatic spreading. For the polarization of macrophages, the role of CCL5/CCR5 is different. Clinical trials using CCR5 inhibition in other cancer entities are underway and the mode-of-action on myeloid cell populations seems to be redundant for other cancer entities. It is true that other chemokines like CCL3 and CCL4 and other receptors like CCR1 probably could compensate the effect of CCR5 inhibition. Analyses in this regard are currently underway. Improved understanding of the complex interplay between the different layers of chemokines (11) and their regulatory role in the local microenvironment will surely yield clinically translatable insights. Animal models and especially rodent models are a typical tool to better understand the functionality of the cells and cytokines involved. For CCR5 inhibition, the gap between animal models and human patients is severe. Published data shows detrimental effects of CCR5 inhibition, leading to a loss of T cell populations and abrogated adaptive immune responses (12). The differences in the plasticity between the innate immune system in rodents and in humans are so severe (13) that our work highlights the translational relevance of this gap. Alternative functional models utilizing fully human cells clearly have their role.

But the complex role and interdependency of the CCL5/CCR5 axis is not limited to the immunological properties, Dr. Mukaida nicely points out the relationship between this axis and the *p53* mutation status. These complexities

of course add to the complexities of the immunological microenvironment and the delicate balance between all these contributing factors on the clinical outcome in a patient under CCR5 inhibition will most likely be different in different cancer entities. More work is necessary.

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