

Development and differentiation of “early-stage” myeloid derived suppressor cells (e-MDSCs) in colorectal cancer – the role of anemia

Colorectal cancer (CRC) is the third most common cancer worldwide. Million new CRC cases were diagnosed in 2020, of which 0.94 million patients died, whereas in 2040, the global number of new CRC cases is predicted to reach 3.2 million. Thus, understanding the mechanisms underlying the development, progression, and treatment resistance of CRC is a vital challenge in modern medicine.

Among leukocytes, the so called myeloid regulatory cells (MRC) constitute a crucial component of TME where the tumor-associated macrophages (TAM), tumor-associated neutrophils (TAN), and myeloid-derived suppressor cells (MDSCs), contribute to cancer progression. MDSCs currently turn attention in the context of their potential targeting in cancer therapy. They accumulate locally in the tumor microenvironment, circulate in the peripheral blood, and are an important element of tumor-induced immunosuppression. MDSCs are composed of three different subpopulations depending on their origin: granulocytic (PMN-MDSCs), monocytic (Mo-MDSCs), and early stage (e-MDSCs). Taken together, MDSCs contribute to tumor evasion of the immune response and promote cancer progression. Although the role and mechanisms of action of Mo-MDSCs and PMN-MDSCs have been investigated for many years now, the origin and exact role of e-MDSCs in cancer development and progression are not known. It is believed that this cell population may differentiate to the other two MDSCs subsets. Very recently, a possible erythroid-to-myeloid trans-differentiation was suggested, where erythroid progenitors lose their developmental potential and switch to the myeloid lineage. One of the key factors associated with this process may be anemia, typically indicated by a lower-than-normal red blood cell (RBC) count and hemoglobin level. In CRC, anemia may be one of the first signs of malignancy and a predictor of poor prognosis of immunotherapy. To date, research on this issue has been conducted on bulk populations, and detailed information on specific cell subsets, including e-MDSCs, is lacking. In this context, it would be interesting to determine whether the population of e-MDSCs is predominantly generated during anemia and whether these cells can differentiate into other MDSCs subsets.

Therefore, the main goal of the proposed research is to verify the role of anemia in the process of MDSCs generation in CRC, especially with respect to the subset of e-MDSC. For this purpose, we will analyze data on the level of MDSCs with and without erythroid markers in patients' blood and tumor material and correlate the results with anemia (developed by the growing tumor or blood loss during surgery) and the tumor stage. Simultaneously, we propose a CITEseq single-cell RNA sequencing analysis of circulating and tumor-infiltrating MDSCs and its correlation with anemia. Furthermore, we plan to use a chemical colorectal cancer mouse model with the induction of anemia, in which we will try to unravel the relationship between anemia and immunosuppression associated with MDSCs and EMCSs, and the possible effectiveness of erythropoietin, used as an anti-anemic drug. Finally, in our work we will focus on deepening the characterization and role of e-MDSCs in CRC, especially to answer if they can differentiate into other MDSCs subpopulations.

Our research has the potential to increase the current state-of-the-art in the field of myeloid regulatory cells in CRC and may bring measurable benefits for patients in the form of possible new forms of treatment targeting the development of these regulatory cells.