The innate immune response serves as the first line of immune defense against invading pathogens and tumors. The focus of our research is to dissect activation modules of innate immune cells, in particular Natural Killer cells and Innate Lymphoid Cells and the influence of the microenvironment on their function in tissues during homeostasis and disease. NK cells are major cytolytic and cytokine producing effector cells that efficiently kill tumors. In contrast to T cells that rely on the recognition of tumor cells via MHC I/tumor associated antigen, NK cells become activated upon integration from signals originating from inhibitory receptors specific for self MHC class I molecules and activating receptors. Accordingly, NK cells efficiently kill tumor cells with low expression of MHC class I. MHC class I deficiency has been reported for many tumors, e.g. in up to 43% of melanoma patients in a recent study, highlighting the potential of NK cells as effector cells against these tumors. So far, NK cell-based therapies such as the adoptive transfer of NK cells or the application of NK engaging mAbs showed benefits in leukemia patients. Adoptive transfer of IL-2-activated NK cells in patients suffering from solid tumors, however, did not result in clinical benefits. In this context, it has been shown that NK cells in tumor tissues display impaired functionality compared to peripheral blood NK cells. Data from many different labs have revealed that tumor infiltrating NK cells express decreased levels of activating receptors, increased levels of inhibitory receptors, are poor producers of IFN-g and exert low cytotoxicity. In our study we elucidated the molecular features of NK cells in tumors. The functional consequences on NK cell activation caused by the tumor microenvironment will be discussed in the talk.

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