☆ 1602 / 10 - Generation of anti-IL-17B antibodies neutralizing IL-17B-mediated alterations of the immune microenvironment, promotion of tumor cell initiating capacity and chemoresistance

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Presenter/Authors

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Disclosures

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Abstract

Interleukin 17B (IL-17B) is a pro-inflammatory cytokine that belongs to a family encompassing 6 interleukins (IL-17A to F) and binds to the IL-17 receptor B (IL-17RB). Recently, amplified IL-17B/IL-17RB signaling was found critical for breast and pancreatic tumorigenesis and elevated expression of IL-17RB has been associated with the shortest survival rates in patients with breast or pancreatic cancer. Using IL-17B knock-out (IL-17B KO) mice we demonstrate here that melanoma, fibrosarcoma and breast cancer cell tumorigenicity is strongly impaired in immunocompetent IL-17B KO mice compared to WT littermates, including a large number of tumor free mice. Reduced tumor incidence in IL-17B KO mice is associated with alterations of the immune tumor microenvironment especially within innate lymphocyte and myeloid sub-populations. We further demonstrate that IL-17B is a key cytokine shaping the tumor initiating cancer cell niche. Indeed, MDA-MB-468 human breast cancer cells overexpressing IL-17B exhibit 10 times higher frequency of tumor initiating cells when xenografted at a serial limiting dilution in nude mice. Tumor progression is, again, associated with alterations of NK cells within the tumor microenvironment and with increased percentages of $CD44^{hi}/CD24^{lo}$ tumor cells, a phenotype associated with breast cancer stem cells (CSC). This is associated with resistance to conventional chemotherapeutic agents such as taxol, an effect that is totally abrogated by disrupting IL-17B-IL-17RB signaling with a neutralizing antibody. Altogether our results point out the key role of IL-17B in regulating the immune microenvironment as well as cardinal features of CSC, one of the alleged causes of resistance to therapy and tumor relapse. Thereby, IL-17B and its receptor appear as potential therapeutic targets for cancer immunotherapy. Collectively, these data support the ongoing development of IL-17B neutralizing antibodies.