A new E3 ubiquitin ligase regulates the immune response in colon cancer

CAMILLE A. SPINNER, ISABELLE LAMSOUL, ARNAUD METAIS, CHRISTEL MOOG-LUTZ, PIERRE G. LUTZ

Institut de Pharmacologie et de Biologie Structurale, IPBS, Université de Toulouse, CNRS, UPS, Toulouse, France

The interactions between tumor cells and their microenvironment have major impact on the evolution of the pathology. In this context, the majority of cancer immunotherapy studies have focused on cytotoxic CD8\(^+\) lymphocyte functions. However, more recently, different reports have highlighted crucial roles of CD4\(^+\) T cell in the anti-tumor immune response. In this study, we have identified the hematopoietic E3 ubiquitin ligase ASB2\(\alpha\) as a novel regulator of CD4\(^+\) T cell driven immunity during tumor development.

We first analyzed ASB2 expression in fresh-frozen primary tumor samples containing tumor, as well as stromal and infiltrating immune cells, from a large cohort of patients with stage I to IV colon cancer. Strikingly, we demonstrate that a high ASB2 expression is associated with a shorter relapse-free survival. To investigate a functional link between ASB2 expression and colon cancer, we induced inflammatory colon tumorigenesis in Asb2 conditional knockout mice (cAsb2\(^{-/-}\)) in which ASB2 inactivation can be induced in hematopoietic cells. Importantly, deletion of Asb2 attenuated the loss of body weight as well as the shortening of the colon and the tumor load. Indeed, the tumors were less numerous and smaller in cAsb2\(^{-/-}\) mice compared to control mice. Taken together, our results indicates that loss of ASB2\(\alpha\) in hematopoietic cells dramatically reduced tumor burden in colitis-associated tumorigenesis. Analysis of immune cells in the colon of tumor-bearing mice revealed a higher recruitment of CD4\(^+\) and CD8\(^+\) T cells associated with higher levels of IFN-gamma in cASB2\(^{-/-}\) mice in comparison to control animals. Indeed, Asb2 is not expressed in T helper-1 (Th1) cells nor in CD8\(^+\) T cells but rather in Th2 cells, thus suggesting that the loss of Asb2 affects the balance between Th1 and Th2 cells. How ASB2\(\alpha\) drives an adaptive immune response that supports tumor development will be discussed.

Altogether, our work evidences a role for ASB2\(\alpha\) in the regulation of the CD4\(^+\) T cell response during tumor development. ASB2\(\alpha\) may therefore represent a novel therapeutic target in cancer.