Society for Immunotherapy of Cancer

FOR IMMEDIATE RELEASE
June 1, 2013

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SITC President Part of Team Reaching Bach2 in Cancer Immunotherapy Treatment

SITC's president, Francessco M. Marincola, MD, in a collaborative project with SITC member Nicholas P. Restifo, MD, as well as many other scientists from several different institutions, recently discovered that a gene called Bach2 may aid in the development of new modalities of cancer immunotherapy by enabling them to turn the body's own immune system against tumors.

"A clue came from the study of autoimmune and allergic disease, where immune responses are targetted at the body's own tissues," said Rahul Roychoudhuri MD of the National Cancer Institute. A number of allergic and autoimmune disorders, such as Crohn's disease, asthma, type I diabetes and multiple sclerosis, are associated with polymorphisms in a gene encoding the transcription factor, BACH2. Despite this, the mechanism Bach2 uses to prevent immune-mediated diseases was not known. To function appropriately, the immune system relies on a delicate balance between immune-stimulating and immune-regulating cells. When immune-stimulating cells become too active, or immune-regulating cells become ineffective, autoimmune and allergic diseases can ensue.

The scientists have now identified Bach2 as a broad regulator of immune activation that stabilizes immune-suppressive regulatory (Treg) cells while limiting the differentiation of multiple inflammatory (effector) lineages in CD4+ T cells.

By studying knockout (KO) mice in which the Bach2 gene had been removed, the investigators were able to evaluate the function of Bach2 in the immune system. While the KO mice appeared normal at birth, they developed a progressive wasting disease that reduced their survival as compared with wild type mice. The disease was accompanied by immune cell infiltration in the lungs and gut of KO mice, and, in particular, there were increased proportions of T helper type 2 (Th2) cells, which are often associated with allergic disease.

Because Bach2 is a transcription factor, the investigators compared gene expression in wild type and KO immune cells. They found very low levels of expression of the Treg cell specific transcription factor FoxP3. As a result, there were very few Treg cells in KO mice, suggesting that Bach2 is required for Treg cell formation. Re-expressing Bach2 in KO cells using gene therapy was able to restore the ability to induce Treg cells, and injection of normal Treg cells into mice with Bach2-deficient immune systems was able to prevent the onset of disease.

By performing massively parallel sequencing using messenger ribonucleic acid (mRNA) and genomic DNA immunoprecipitated using antibodies specific for Bach2, the investigators were able to identify genes directly regulated by Bach2. Bach2 repressed genes associated with differentiation of CD4+ T cells into Th1, Th2 and Th17 effector cell lineages. Consequently, in conditions that normally induce Treg cells, Bach2-deficient cells became effector cells. Treating the cells with effector cytokine-blocking antibodies partially rescued induced Treg formation in the KO cells. Moreover, KO T cells grown in conditions that induce effector differentiation expressed higher levels of effector lineage-associated cytokines.

Taken together, these studies show that Bach2 plays a critical role in restricting pro-inflammatory programs not only in developing Treg cells but also in effector T cells. Because of its broad role in regulating immune activation, Bach2 is an attractive target for the development of new treatments for autoimmune and allergic diseases.

“Modulation of Bach2 may also be useful in the treatment of cancer since regulatory T cells are often co-opted by tumors to protect themselves from attack by the immune system,” said Restifo. Identification of factors which skew the balance between inflammatory and regulatory immune activity will pave the way for the development of novel immunotherapies that tip the balance of immunity in the favor of tumor destruction.

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