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REVIEW ARTICLE

Regulation of immune responses, apoptosis, and tumorigenesis by separate FOXP-3-dependent genes: Connection with clinical manifestations

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Recently, forkhead/winged-helix family box protein P3 (FOXP-3) was described as the main regulator of regulatory T cells' activity. This transcription factor has the ability to control the immunosuppressive response of regulatory T cells. FOXP-3 has binding sites for different genes specific for proteins with various important functions. In this article, selected FOXP-3-dependent genes with known functions were divided into two groups. The first group of genes has main immunoregulatory functions, and the second group has the ability to regulate apoptosis and tumorigenesis. Investigation of the functions of all FOXP-3-dependent genes opens perspectives for applications in different fields of basic and clinical research.

Introduction

Regulatory T cells (Tregs) are a subpopulation of $CD4^+$ cells and primarily maintain the immune system homeostasis of the organism. These cells have a high immunosuppressive potential for both innate and adaptive immunities. Disturbance of the cellular homeostasis results in either self-reactive autoimmune aggression or immune deficiency. The investigation of T cells with suppressive activity began in 1970, when new subpopulation of T-lymphocytes with immunosuppressive properties was first described.[1] Since this initial observation, numerous articles characterizing T cells with immune regulatory properties have been published; however, the mechanisms inherent to the immune response in these cells have not been fully elucidated.

Forkhead/winged-helix family box protein P3 and immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

The immune response that characterizes Tregs is realized through the action of the forkhead/winged-helix family box protein P3 (FOXP-3) (Scurfin). The functional activity of

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$CD4^+CD25^+$ Tregs depends on the high expression of FOXP-3 gene and protein. FOXP-3 is a homodimer consisting of a proline-rich domain at the N-terminus in addition to a C2H2 zinc finger and a leucine zipper located in the center of the amino acid sequence. This central domain participates primarily in protein—protein interactions, whereas the C-terminal end of FOXP-3 is a forkhead DNA-binding domain. FOXP-3 has regions that allow it to bind to approximately 700 genes and intergenically encoded microRNAs. In addition, FOXP-3 may have opposing effects on different genes, facilitating the transcription of some genes while repressing the transcription of others. Changes or defects in the coding sequence of the FOXP3 gene result in the development of different pathological conditions. Complete inactivation of FOXP3 gene because of a condition known as immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. IPEX syndrome is very rare in humans and has only been observed in male patients. This syndrome is characterized by a number of complications, including diarrhea, a failure to thrive, eczema, atopic psoriasiform dermatitis, alopecia, hemolytic anemia, thrombocytopenia, neutropenia, hypo- or hyperthyroidism, lymphoadenopathy, Type 1 diabetes mellitus, and increased susceptibility to infections. Other clinical complications may include respiratory distress, bruising, hypocalcemia, hepatic parenchymal disease, cholestasis, hypertension, cardiomegaly, glomerulopathy, encephalopathy, and testicular atrophy. IPEX animal models show a phenotype characteristic of the scurfy mouse.[2] These animals have scaly skin, progressive anemia, thrombocytopenia, leucocytosis, lymphoadenopathy, various infections, diarrhea, gastrointestinal injury, cachexia, and hypogonadism in males, and they typically die within the first few weeks after birth. FOXP-3-related activation of Tregs has been demonstrated by the hypersensitivity of scurfy mice to activation through the T cell receptors.[3] Different changes of the regulation control by the FOXP-3 of FOXP-3-dependent genes result in alteration of Tregs functions and also because of further specific autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, ulcerative colitis, Crohn's disease, celiac disease, hemolytic anemia, and asthma.[4] All genetic abnormalities that result in the onset of the IPEX syndrome and other selective syndromes as a consequence of mutations in genes dependent on FOXP-3 can be explained mainly by unspecific autoimmune aggression that is attributed to some aspects of the regulation of T cells and also the misbalance of regulation of FOXP-3-dependent genes, which is the result of separate manifestations of IPEX syndrome. In recent reports by Sugimoto et al. (2006),[5] Zheng et al. (2007),[6] and Hill et al. (2007),[7] these authors were the first who indicated the presence of FOXP-3-related genes in natural and induced Tregs by detecting differences in marker genes in $CD4^+CD25^-$ and $CD4^+CD25^+$ cells.[5–7]

In this article, 10 genes were selected from all FOXP-3-dependent genes detected in the investigations of Sugimoto et al. (2006),[5] Zheng et al. (2007),[6] and Hill et al. (2007)[7] in connection with any of the following criteria: high degree of down- or upregulation of separate gene expression after functional activation of Tregs and high FOXP3 gene expression; proof of synchronous expression of FOXP3 gene and protein and selected gene expression by other authors; and the importance of genes in regulations of immune reactions and $CD4^+CD25^+$ cells functions. The genes described were divided into two groups: one of them is a group of genes capable of changing the immune response and the other group includes genes that may regulate apoptosis and tumorigenesis. The influence [induction (+) or inhibition (−)] of high expression of FOXP-3 on every described gene expression is indicated in Table 1.

Immune response regulation

The main function of FOXP-3 is to influence Tregs activity and, as a result, there is a possibility to regulate the activity of the immune reactions. The group of FOXP-3-dependent genes that are known to code separate proteins that may change the immune response was indicated. FOXP-3 may change expression of these genes because of suppression or activation of immune response members. The most well-known genes from the aforementioned group include the cytotoxic T-lymphocyte-associated 4 (CTLA-4); inducible costimulator (ICOS); cyclic Adenosine Monophosphate-responsive element modulator (CREM); and PR [positive regulatory domain I—binding factor 1 (PRDI-BNF1)-RIZ] domain containing 1, zinc finger (PRDM1) genes.[5–7]

Cytotoxic T-lymphocyte-associated 4

The CTLA-4 protein is coded by CTLA-4 gene, and it is similar to the lymphocyte CD28 molecule structure, with the exception that it is more competitive than CD28. CTLA-4 has a higher binding affinity to CD80 (B7.1) and CD86 (B7.2) in antigen-presenting cells.[8] Furthermore, inhibition of monocytes and macrophages by CTLA-4 is one of the primary mechanisms to repress the immune response by Tregs.[9] The up-expression of this receptor protein is also regulated by the FOXP-3 protein in natural and induced Tregs.[10] Interestingly, the application of the CTLA-4 antibody or specific deficiency of CTLA-4 caused the expected effects of severe yet reversible T cell-mediated autoimmune disease.[11] The low level of CTLA-4 expression was observed in patients with juvenile idiopathic arthritis.[12] Some human studies had shown that the administration of antibody to CTLA-4 resulted in tumor necrosis.[8]

Inducible costimulator

Another marker of FOXP-3 activity is ICOS.[13] The ICOS gene codes a protein ICOS, which participates in T cell receptor stimulation of T cells. In this case, CD28 is not required for the induction of ICOS. Data have indicated that there is an association between the expression of ICOS and the production of some cytokines. High expression of ICOS was correlated with the production of interleukin (IL)-10 in Tregs.[14] Two subpopulations of $CD4^+CD25^+$ natural Tregs were detected. One subset expressed ICOS and another ICOS-negative subpopulation of Tregs. The $ICOS^+$ Tregs produced IL-10 and transforming growth factor (TGF)-β to suppress T cells and dendritic cells. The $ICOS^-$ Tregs produced TGF-β only to suppress T cells. Development of Type 1 diabetes mellitus and common variable immunodeficiency was associated with disturbances of ICOS expression in Tregs.[15]