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News & Views

Regulatory T cell, the peacekeeping force in host defense system, received Nobel Prize in Physiology or Medicine, 2025

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INTRODUCTION

Arrogance versus tolerance in immune system

In an editorial of the journal, Science, Daniel E. Koshland Jr. stated that "the mechanisms of self-versus non-self-recognition in the immune system ranks at or near the top of all the mysteries in modern science" (Koshland, 1990). We know very well that self-non-self-discrimination plays key role in host defense system by which vertebrate species can detect foreign invaders and act against it without causing harm to its own cells. Invariably foreign invaders appear differently than our own body cells yet invaders many exhibit similarities with human cells, so there must be some critical judging ability of our defense system to attack the true invaders and rescue its own cells. Vertebrate immune system is rendered tolerant to their own cells by two processes, one is "clonal deletion" of self-reactive immune cells (T & B cells) and another that results in their inactivation called "clonal anergy" (Ramsdell & Fowlkes, 1990). In simple language we can say that immune system keep track of what to attack? And what to protect? However, many a time, decision making process to distinguish self from non-self is not so absolute. We may be curious to know why the immune system does not attack our bodies more frequently? It is because a regulatory cell known as Treg cell which act as Peace keepers of the Immune System calm down the aggression behaviour of the troops (Fehervari & Sakaguchi, 2006).

More to spell on T cell

A subpopulation of lymphocyte which originates from uncommitted hematopoietic stem cells and finally undergo maturation within the microenvironment of thymus are known as T cell ("T" represents for thymus). Uncommitted cell receives primary education in thymus (primary lymphoid organ), so that these cells learn to rearrange their gene pools. Finally these cells are released in peripheral circulation as highly committed educated cells, called matured T cells. Matured T cells having some membrane bound receptors (TCR T cell receptor) along with certain signature molecule (T cell marker) as their mark of identity. These receptors are unique in nature and never exhibit overlapping character. Those receptors are of different shape like jigsaw piece, thereby any individual could make more than 10^{15} different T-cell receptors from its germline DNA. This explanation stands against "one gene one receptor concept", but it is very true in case of T and B cell but not in any other somatic cells. Simply these receptors act as sensor to detect invaders. Human immune system very well reacts and responds to foreign protein but rarely towards its own (self). Why so? It is because from embryonic stage within mother's womb whatever self-reacting lymphocytes originated incidentally or accidentally within thymic environment are removed by a process known as programmed cell death for which scientific terminology is apoptosis. Fortunately, during physiological process of T cell development, those T cells expressing high affinity receptor for self-antigen are eliminated by negative selection process called central immune tolerance (Xing & Hogquist, 2012). With the above explanation can we expect that, all the self-reactive lymphocytes have been eliminated before birth and there is no threat from immune system to react against self-protein in their adult life? Unfortunately, this is not so happy situation; rather some amount of self-reacting lymphocytes are still escaped from apoptosis and keep on circulating in blood stream that can cause danger in adult life. To achieve self-tolerance, the immune system enlists numerous safeguard mechanisms. Very often antibodies against self-antigens are produced for which valid justification is not always available. If this is true then how we are not suffering from autoimmune disease? Why the immune system does not attack our bodies more frequently? This may be due to gift of Treg cells.

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Autoimmune disease is the condition in which the host immune system reacts against its own tissues and organ that leads to set inflammation and finally the functional property of that organ is destroyed. Treg-mediated robust immunosuppression provides self-tolerance and protection against autoimmune diseases (Goswami et al., 2022). Most common example of autoimmune disease in human is type-1diabestes. In type-1 diabetes, the body's own immune system mistakenly destroys the insulin-producing cells in the pancreas. Genetical inheritance of individual also plays some definite role in this process, thereby, few suffers and few differs. Rheumatoid arthritis is also another common disease that is grouped under autoimmune disease. In 1995, Shimon Sakaguchi a distinguished Professor from Osaka University, Japan, proposed a new subpopulation of suppressor T cells bearing CD4 marker as regulatory T (Treg) cells (Sakaguchi et al., 1995). Tregs also play a crucial role in immune homeostasis and self-tolerance (Mikami et al., 2020). The Treg cells prevent these accidental attacks by the immune system against the body's own cells concurrently when this regulatory process goes wrong autoimmune diseases arise. These Treg cells also influence the immune system's response to infectious agents, cancer, organ transplants and pregnancy. It is also not easy to explain why in presence of self-reactive lymphocyte in circulation, few never exhibit sign of autoimmune disease, while a few suffer (Matzinger et al., 2002). In the present year, the subject of T regulatory cells has taken the center stage in scientific discovery for which three scientists namely Mary E. Brunkow (USA), Fred Ramsdell (USA) and Shimon Sakaguchi (Japan) has been crowned with Nobel Prize in physiology or medicine for their contribution in this regard. The work of the Nobel Laureates has paved the path for the treatments for cancer and autoimmune diseases in human population.

Scientific career of prize winner

Born in 1961, **Mary E. Brunkow** received bachelor's degree in molecular and cellular biology in 1983 from the University of Wisconsin. In 1991, she earned a doctorate from Princeton University in Princeton, USA. Brunkow was keen to probe why a specific mouse strain (scurfy mouse) was particularly vulnerable to autoimmune diseases. According to their finding, a point mutation in a gene, that they named Foxp3, forkhead box genes was responsible for immunodeficiency. Presently Brunkow works as a senior program manager at the Institute for Systems Biology in Seattle.

Fred Ramsdell, born in December 4, 1960 at Elmhurst, Illinois, U.S. In 1983, he received his bachelor's degree graduate in biochemistry and cell biology. Ramsdell, obtained PhD at University of California Los Angeles in 1987. At the time of the award, he is affiliated with Sonoma Biotherapeutics, San Francisco, CA, USA. In 2001, Ramsdel along with Brunkow revealed that mutations in the FOXP3 gene caused a disease called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) in human and the mutation in FOXP3 gene is also responsible for ill health in scurfy mice (Brunkow et al., 2001).

Shimon Sakaguchi born in 1951, received M.D. in 1976 and Ph.D. in 1983 from Kyoto University, Japan. After ten years of his continouus effort, he published a paper in 1995 setting out his discovery of regulatory T-cells which can calm the immunesystem. These cells are characterised by CD4+ marker along with CD25 marker on its surface. Using Balb/c athymic nude mice (nu/nu), he could able to establish the pivotal role played by Treg cells to maintain immunetolerance (Sakaguchi et al., 1995). He is a distinguished Professor at the Immunology Frontier Research Center, Osaka University, Japan

Origin and its cousins of Treg cell .

Treg cells are generated from the multipotent hematopoietic stem cell (HSCs). These HSCs also give rise to other sets of lymphocytes. Treg cells express specific distinguishing molecules on its membrane along with common CD markers for T cells. To be more precise the CD stands for cluster of differentiation. These clusters are membrane bound protein molecules expressed on the surface of leukocytes that act as receptors which can bind with some other protein molecules, called ligand. During development, initially T cells are double negative lacking both CD4 and CD8 marker and subsequently on differentiation these cells acquire double positive character to express both CD4+ and CD8+ marker. Ultimately due to positive selection, these cells gain mutually exclusive single positive character to be either CD4+ or CD8+ cells. Out of these few CD4+ T cells acquire distinct phenotypic marker and designated as Treg cell. Thymic

stromal cells including cortical medullary thymic epithelial cells and dendritic cells contribute the development of Treg cells differentiation and selection. Treg cells leave the thymus, enter the circulation to patrol and control the autoimmune reaction. Additionally, both IL-2 and IL-7 in the thymic microenvironment are essential for T cell development (Josefowicz et al., 2012). The abbreviation IL stands for interleukin. These are soluble protein molecules secreted from leukocytes and other cells too, act locally so that intercommunication continue between cells, essentially required for cellular biological functions. The Treg cell can quench adaptive immune response, and can inhibit the proliferation of other cells (*in vitro* and *in vivo*). Therefore, it suppresses auto-reactive immune response. This is called a peripheral tolerance. If any autoreactive T cells exist in circulation which has not been eliminated during thymic selection and ready to act aggressively against self-protein, in that situation the Treg cell must calm down the attack and protect the body from devastation. What control this selection is yet to be discovered, however, presently two populations of Treg cell have been established, one of them is natural Treg cell and another cousin is induced Treg cell or adaptive Treg cell. Treg cells can be generated under the influence of specific cytokine such as TGFβ (T cell growth factor beta) and IL-10 cytokine (Bluestone & Abbas, 2003). The term cytokine and interleukin are used in synonymous way.

Clarity on Treg identity

Treg cells can be considered as CD4 marker bearing T cells, constitutively expressing transcription factor Foxp3 protein (forkhead boxP3), along with CD25 (IL-2Rα, i.e. high affinity receptor for IL-2), and CTLA4 (cytotoxic T lymphocyte antigen 4). As early as 13 weeks of gestation in human, the Treg cells are found in thymus and express *forkhead family* transcription factor Foxp3 protein. Out of all these markers Foxp3 is more specific, whereas CD25 and CTLA4 are less specific and expressed on conventional T cells. Each of these molecules have distinct role on its survival and biological activity (Darrasse et al., 2005). More elaboration about the role of these markers may not be interesting for the readers and hence eliminated in the present discussion.

Glean on Foxp3 protein

For description of Foxp3 protein, it is imperative to spell out its discovery and original work. During 1949 at Oak Ridge National laboratory, a spontaneous scurfy mutation in mice was observed. Subsequent study revealed that the mutation is X linked and only males are affected X^{sf}/Y. Homozygous male carrying the mutant X chromosome exhibits this syndrome whereas heterozygous female carriers of the mutant X chromosome allele are healthy. Scurfy mice have thickening and scaling of the ears, eyelids, feet, tail and severe runting (Ziegler et al., 2006). Internal organ has characteristic lymphadenopathy, splenomegaly, hepatomegaly and massive lymphocytic infiltration in the skin and liver. These lesions are closely resembled like the graft-versus–host reaction. Initial study uncovered that mutation in scurfy mice is affecting gene encoding Foxp3 protein and can be rescued by introducing transgene for wild type Foxp3 allele. Conventional T cell does not express Foxp3 protein under normal physiological condition where as high expression is found in some population of CD25+ CD4 + cells. Ectopic expression of Foxp3 protein in isolated $CD4^+/CD25^+$ T cells leads to acquisition of suppressor function in non-regulatory T cells. In the similar way, introduction of Foxp3 gene in naïve T cell confers suppressive function. Adaptive transfer of Treg cell can rescue neonatal Foxp3 deficient mice from the disease. Mice when experimentally subjected to delineate the germ line Foxp3 gene progressively express autoimmune lesions. Even deletion of Foxp3 gene from thymic and dendritic cell which shape the repertoire of developing T cells did not have any effect on dysregulation or alteration in T cell differentiation. Similarly, deletion of Foxp3 gene in macrophage did not affect the tumor growth. These indicate that the role of Foxp3 is not affecting any other cells except T cells (Josefowicz et al., 2012).

Demonstration of Treg mediated suppression

In vitro co-culturing CD4+ CD25+ Treg cell in the presence of APC (antigen presenting cells) and other antigen specific CD4 and CD8 responder cells along with specific antigen resulted suppression of proliferation of responder cell and reduced IL-2 production. Treg cell expressing high number of IL-2 receptor on its surface helps to *stopping up* the IL-2 produced from responding T cells thereby preventing their proliferation. This has been confirmed in other experiment in which effector T cell undergo apoptosis after exposure to Treg cells. The suppression activity is supposed to be due to contact dependant mechanism and confirmed when the Treg and responder cells were separated by semi-permeable membrane; the suppressive effect was abrogated. The possible mechanism of this contact mediated suppression is due

to up regulating intracellular cytoplasmic cyclic AMP that leads to inhibitory effect on T cell proliferation by contact through gap junction (Bopp et al., 2004). Contrary to this explanation imaging studies have shown that T effector cells do not interact stably with Treg cells during suppression *in vivo* and *in vitro* experiment (Tang et al., 2006). Others are of opinion that effecteor T cells are eliminated due to lethal effect of granzyme and perforin released from Treg cells (Grossman et al., 2004). Researchers are of opinion that Treg cell may interfere the antigen presenting ability of DC (dendritic cells) or promote secretion of suppressive factor from DC, one of them is indolamine 2, 3 dioxygenase (IDO) a potent immunosuppressive enzyme. IDO induction is dependent upon high expression of inhibitory receptors CTLA4 on Treg cell. The mechanism is too complex and conclusive effect of CTLA4 is difficult to prove. Blocking CTLA4 has no effect on Treg cells in most circumstances either *in vitro* or *in vivo* experimentation. Treg cells from CTLA4 deficient mice exhibit similar suppressive effect like that of wild partner. On the contrary *in vivo* blocking of CTLA4 activity in mice can abrogate Treg mediated suppression of IBD autoimmune gastritis and transplantation (Wing and Sakaguchi, 2010).

Conclusion

The discovery of Treg cells has added clear understanding of how the immune system functions and why all the individuals do not develop serious autoimmune diseases. Subject of human T regulatory cell as therapeutic agents is presently considered as a new area of research in clinical application for human medicine. Like many other white blood leukocytes, Treg cells is primarily the peace keeping force as well body's security guards. In summary, the responsibility of Treg cell is to prevent other T cells from mistakenly attacking the body's own cells rather to tolerate the own cells through peripheral immune tolerance. Regulatory T cells also ensure the immune system to calms down after it has eliminated an invader. So it does not act aggressively, similarly never allow working progressively at high speed. We can say Treg cell acts as brake on immune-system, so the system does not move further in an uncontrolled manner. The plasticity and heterogeneity in Treg cells population derived from mice and human species has added new information in Treg cell biology. Due to mutual exclusive and conflicting findings from different laboratory, it is yet not clear at what extent these cells contribute in different disease models. Isolation of Treg cells is not so easy due to lack of specific marker for experimental purpose. Human Treg cells expressing low, intermediate, or high level of CD25 molecule is difficult to isolate as these differential boundaries are too thin. One thing has been exclusively confirmed that Treg cells express specific transcription factor such as Foxp3 protein which is considered as master regulator.

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