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Review on Immune Tolerance Mechanism and Physiology

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Received: 12 December 2017 Accepted: 4 January 2018 Published: 15 January 2018

Abstract

Immunological tolerance is classified into central tolerance or peripheral tolerance depending on where the state is originally induced in the thymus and bone marrow (central) or in other tissues and lymph nodes (peripheral).The mechanisms by which these forms of tolerance are established are distinct, but the resulting effect is similar. The recognition of antigens by the immature B cells in the bone marrow is critical to the development of immunological tolerance to self. This process produces a population of B cells that do not recognize self-antigens but may recognize antigens derived from pathogens or non self. T cells are selected for survival much more rigorously than B cells. They undergo both positive and negative selection to produce T cells that recognize self-MHC molecules but do not recognize self-peptides. Since, central tolerance is not 100

Index terms— autoimmunity, central, immune, peripheral, physiology, tolerance.

1 I. Introduction

mmunological tolerance is describes a state of unresponsiveness of the immune system to substances or tissue that has the capacity to elicit an immune response (Michael and Ronald, 2011). Immune tolerance encompasses the range of physiological mechanisms by which the body reduces or eliminates an immune response to particular agents (Warrington et al., 2011). It is used to describe the phenomenon underlying discrimination of self from non-self, suppressing allergic responses, allowing chronic infection instead of rejection and elimination, and preventing attack of fetuses by the maternal immune system (Tizared, 2013). Diverse innate immune cells including NK cells, DC and mast cells exert a variety of immune-regulatory mechanisms important for the induction of tolerance. These mechanisms include regulating T-cell activation and differentiation through cytokine production, the elimination of donor APCs, and inhibition or killing of effecter T cells (Murphy et al., 2011).

Historically the phenomenon of immune tolerance was first described by Ray D. Owens in 1945, who noted that dizygotic twin cattle sharing a common placenta interestingly shared a stable mixture of each other's red blood cells and retained that mixture throughout life. Although Owens did not use the term immune tolerance, his study showed the body could be tolerant of these foreign tissues. This observation was experimentally validated by Rupert E. Billingham and Peter Medawar in 1953, which showed by injecting foreign cells into fetal or neonatal mice, they could become accepting of future grafts from the same foreign donor. Interestingly, though, they were not thinking of the immunological consequences of their work at the time. However, these discoveries and the host of allograft experiments and observations of twin chimerism they inspired were seminal for the theories of immune tolerance formulated by Sir Frank McFarlane Burnet and Frank Fenner, who was the first to propose the deletion of self-reactive lymphocytes to establish tolerance, now termed clonal deletion. Burnet and Medawar were ultimately credited for the discovery of "acquired immune tolerance" and shared the Nobel Prize in Physiology or Medicine in 1960 (Pelanda et al., 1996;Hardy et al., 1991).

Immune tolerance is important for normal physiology. Central tolerance is the main way the immune system learns to discriminate self from non-self. Peripheral tolerance is key to preventing over reactivity of the immune system to various environmental entities like allergens, gut microbes, and others (Tizared, 2013). Deficits in central or peripheral tolerance also cause autoimmune disease, resulting in syndromes such as systemic lupus

erythematosus, rheumatoid arthritis, type 1 diabetes, autoimmune polyendocrine syndrome type 1 (APS-1), and immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX), and potentially contribute to asthma, allergy, and inflammatory bowel disease (Hardy et al., 1991). Immune tolerance, however, also has its negative tradeoffs. It allows for some pathogenic microbes to successfully infect a host and avoid elimination. In addition, inducing peripheral tolerance in the local microenvironment is a common survival strategy for a number of tumors that prevents their elimination by the host immune system (Roberta and Torres, 2015). Therefore the objective of this paper is to review you with the concept of immunological tolerance in physiology.

2 II. Central and Peripheral Tolerance

Immunological tolerance is classified into central tolerance or peripheral tolerance depending on where the state is originally induced in the thymus and bone marrow (central) or in other tissues and lymph nodes (peripheral) (Roberta and Torres, 2015;Tizared, 2013). The mechanisms by which these forms of tolerance are established are distinct, but the resulting effect is similar.

Central tolerance refers to the tolerance established by deleting autoreactive lymphocyte clones before they develop into fully immunocompetent cells (Tizared, 2013). It occurs during lymphocyte development in the thymus and bone marrow for T and B lymphocytes, respectively. In these tissues, maturing lymphocytes are exposed to self-antigens presented by medullary thymic epithelial cells, thymic dendritic cells, or bone marrow cells (Warrington et al., 2011). At the level of bone marrow the germ line gene rearrangement and inability call to express surface marker (B cell, 220B/ CD44) is order for progenitor B cell tolerance in the bone marrow (Roberta and Torres, 2015).

Those lymphocytes that have receptors that bind strongly to, or "recognize," self-antigens are removed by induction of apoptosis of the autoreactive cells, or by induction of anergy, a state of non-activity. Weakly autoreactive B cells may also remain in a state of immunological ignorance where they simply do not respond to stimulation of their B cell receptor. Some weakly self-recognizing T cells are alternatively differentiated into natural regulatory T cells (nTreg cells), which act as sentinels in the periphery to calm down potential instances of T cell autoreactivity. This process of negative selection ensures that T and B cells that could initiate a potent immune response to the host's own tissues are eliminated while preserving the ability to recognize foreign antigens (Roberta and Torres, 2015).

Peripheral tolerance develops after T and B cells mature and enter the peripheral tissues and lymph nodes. It is established by a number of partly overlapping mechanisms that mostly involve control at the level of T cells, especially CD4 + helper T cells, which orchestrate immune responses and give B cells the confirmatory signals they need in order to produce antibodies (Nemazee, 2017). Inappropriate reactivity toward normal self-antigen that was not eliminated in the thymus can occur, since the T cells that leave the thymus are relatively but not completely safe (Warrington et al., 2011). Some will have receptors (TCRs) that can respond to self-antigens that are present in such high concentration outside the thymus that they can bind to "weak" receptors and the T cell did not encounter in the thymus (such as, tissue-specific molecules like those in the islets of Langerhans, brain, or spinal cord not expressed by AIRE in thymic tissues). Those self-reactive T cells that escape intrathymic negative selection in the thymus can inflict cell injury unless they are deleted or effectively muzzled in the peripheral tissue chiefly by nTreg cells (Tizared, 2013).

3 a) Mechanisms of B Cell Tolerance

The recognition of antigens by the immature B cells in the bone marrow is critical to the development of immunological tolerance to self. This process produces a population of B cells that do not recognize selfantigens but may recognize antigens derived from pathogens (non-self). Immature B cells expressing only surface Ig M molecules undergo negative selection by recognizing self-molecules present in the bone marrow. This antigen induced loss of cells from the B cell repertoire is known as clonal deletion (Akiyama et al., 2005).

B cells may encounter two types of antigen, multivalent cell surface antigens or low valence soluble antigens: (1) When immature B cells express surface Ig M that recognizes ubiquitous self -cell-surface (i.e. multivalent) antigens, such as those of the MHC they are eliminated by a process known as clonal deletion. These B cells are believed to undergo programmed cell death or apoptosis. (2) Immature B cells that bind soluble selfantigens (i.e. low valence) do not die but their ability to express Ig M on their surfaces is lost (as a result of the downregulation in receptor synthesis due to the development of receptor tolerance similar to the process seen in drug tolerance through constant exposure to self-antigen). Thus, they migrate to the periphery only expressing IgD (pushed by the division of additional B cells) and are unable to respond to antigen. These B cells are said to be anergic (Nemazee, 2017;Tizared, 2013;Akiyama et al., 2005;Klinman, 1996).

Only B cells that do not encounter antigen whilst they are maturing in the bone marrow can be activated after they enter the periphery. These cells bear both IgM and IgD receptors and constitute the repertoire of B cells that recognize foreign antigen. Even if mature self-reacting B cells were to survive intact, they would very rarely be activated. This is because B cells need co-stimulatory signals from T cells as well as the presence of its recognized antigen to proliferate and produce antibodies (Peripheral tolerance). G negative selection to produce T cells that recognize selfmajor histocompatibility complex (MHC) molecules but do not recognize self-peptides. T cell tolerance is induced in the thymus (Tizared, 2013). Positive selection occurs in the thymic cortex. This

process is primarily mediated by thymic epithelial cells, which are rich in surface MHC molecules. If a maturing T cell is able to bind to a surface MHC molecule in the thymus, it is saved from programmed cell death; those cells failing to recognize MHC on thymic epithelial cells will die. Thus, positive selection ensures that T cells only recognize antigen in association with MHC. This is important because one of the primary functions of T cells is to identify and respond to infected host cells as opposed to extracellular pathogens (Bose et al., 2003). The process of positive selection also determines whether a T cell ultimately becomes a CD4+ cell or a CD8+ cell: prior to positive selection, all thymocytes are doubling positive (CD4+CD8+) i.e. bear both co-receptors. During positive selection they are transformed into CD4+CD8-or CD8+CD4-T cells depending on whether they recognize MHC II or MHC I, respectively (Bose et al., 2003).

T cells also undergo negative selection in a process analogous to the induction of self-tolerance in B cells, this occurs in the cortex, at the cortico-medullary junction, and the medulla (mediated in the medulla predominately by medullary thymic epithelial cells (mTECs) and dendritic cells). mTEC display "self" antigens to developing T-cells and signal those "selfreactive" T-cells to die via programmed cell death (apoptosis) and thereby deleted from the T cell repertoire. This process is highly dependent on the ectopic expression of tissue specific antigens (TSAs) which is regulated by the autoimmune regulator (Lahl et al., 2007).

This clonal deletion of T cells in the thymus cannot eliminate every potentially self-reactive T cell; T cells that recognize proteins only found at other sites in the body or only at certain times of development (e.g. after puberty) must be inactivated in the periphery. In addition, many self reactive T cells may not have sufficient affinity (binding strength) for the self antigen to be deleted in the thymus (Tizared, 2013;Lahl et al., 2007).

The first opportunity to eliminate self-reactive T cells occurs in the thymus, where thymocytes undergoing high avidity interactions with APCs presenting a self-antigen are eliminated by clonal deletion. Thymocytes experiencing interactions with APCs that while not strong enough to trigger cell death are sufficiently strong to indicate an unacceptable level of self-reactivity may undergo induction of anergy, TCR revision, or be diverted into alternative lineages, such as FoxP3 + regulatory T cells or CD8? T cells instead of undergoing deletion (Akirav et al., 2011).

Despite the numerous mechanisms of central tolerance, it is clear that self-reactive T cells still escape to the periphery. This may occur stochastically for some thymocytes simply because they did not encounter the limited number of APCs expressing their cognate ligand as they matured in the thymus. In other cases, the avidity between the self-reactive thymocyte and the APC presenting the self-antigen may not be quite high enough to trigger the normal mechanisms of central tolerance. Low avidity interactions may occur because the TCR has relatively low affinity for the peptide/MHC complex. Alternatively, the peptide may have low affinity for the MHC molecule, and this unstable interaction may result in a low abundance of peptide/MHC complexes available on the APC cell surface (Kretschmer et al., 2005).

Normally, these low avidity interactions would not pose a threat when the T cells enter the periphery, as the threshold for T cell activation in the periphery is believed to be higher than the threshold for induction of central tolerance. However, T cells with low avidity for their self-antigen/ MHC complex could contribute to autoimmunity if the abundance of self-antigen/ MHC complexes increases in the periphery relative to the amount found in the thymus, or a post-translational modification of the self-antigen occurs in the periphery that increases the affinity of the TCR for the selfantigen/MHC complex (Gardner et al., 2009).

Furthermore, antigens that are developmentally expressed may not be present in the thymus when some thymocytes are subjected to negative selection, resulting in a failure to induce central tolerance. Cells expressing these antigen/MHC complexes later in life could become the targets of self-reactive T cells that matured in the thymus and entered peripheral circulation prior to the expression of the self-antigen (Shimon et al., 2008).

4 c) Immune Tolerance in Physiology the Case of Maternal Embryo Recognition

Immune tolerance is important for normal physiology. Central tolerance is the main way the immune system learns to discriminate self from non-self (Roberta and Torres, 2015). The fetus has a different genetic makeup than the mother, as it also translates its father's genes, and is thus perceived as foreign by the maternal immune system. Women who have borne multiple children by the same father typically have antibodies against the father's red blood cell and major histocompatibility complex (MHC) proteins. However, the fetus usually is not rejected by the mother, making it essentially a physiologically tolerated allograft **??**Noronha and Actczak, 2010).

It is thought that the placental tissues which interface with maternal tissues not only try to escape immunological recognition by downregulating identifying MHC proteins but also actively induce a marked Review on Immune Tolerance Mechanism and Physiology peripheral tolerance. Placental trophoblast cells express a unique Human Leukocyte Antigen (HLA-G) that inhibits attack by maternal NK cells. These cells also express IDO, which represses maternal T cell responses by amino acid starvation (Petroff et al., 2002).

Maternal T cells specific for paternal antigens are also suppressed by tolerogenic DCs and activated iTregs or cross-reacting nTregs. Some maternal Treg cells also release soluble fibrinogen-like proteins 2 (sFGL 2), which suppresses the function of DCs and macrophages involved in inflammation and antigen presentation to reactive T cells These mechanisms altogether establish an immune-privileged state in the placenta that protects the fetus. A break in this peripheral tolerance results in miscarriage and fetal loss (Hunt and Robertson, 1996).

The maternal immune system has to balance the opposing needs of maintaining robust immune reactivity to protect both mother and fetus from invading pathogens, while at the same time tolerating highly immunogenic paternal alloantigens in order to sustain fetal integrity. Regulatory T cells are responsible for the establishment of tolerance by modulating the immune response and uterine natural killer cells direct placentation by controlling trophoblast invasion. A variety of other cell types, including decidual stromal cells, dendritic cells, and immunomodulatory multipotent mesenchymal stromal cells, are found at the fetalmaternal interface. These cells conspire to establish a suitable environment for fetal development without compromising systemic immunity (Suano et al., 2011). Defects in any of these components can lead to gestational failure despite successful fertilization.

5 III. Conclusions

Immunological tolerance is classified into central tolerance or peripheral tolerance depending on where the state is originally induced in the thymus and bone marrow (central) or in other tissues and lymph nodes (peripheral). The mechanisms by which these forms of tolerance are established are distinct, but the resulting effect is similar. The recognition of antigens by the immature B cells in the bone marrow is critical to the development of immunological tolerance to self. This process produces a population of B cells that do not recognize self-antigens but may recognize antigens derived from pathogens (non-self). T cells are selected for survival much more rigorously than B cells. They undergo both positive and negative selection to produce T cells that recognize self-MHC molecules but do not recognize self-peptides. Because central tolerance is not 100% efficient, mechanisms of peripheral T-cell tolerance are required to prevent autoimmunity. Active peripheral tolerance is maintained by numerous types of regulatory T cells, the best known of which are FoxP3 + Tregs that develop naturally in the thymus or can be induced in the periphery. Immune tolerance is important for normal physiology. Central tolerance is the main way the immune system learns to discriminate self from nonself which is clearly stated in the case of early embryo communication within placental barrier. Recent research reveals the cellular and molecular basis of immune tolerance development and function and implicates deregulations of immunological disease and treatment option further study and recommendation is must to have comprehensive immunological idea on normal physiology and autoimmune disorder treatment. [1]

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