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On the Physiology of Immune System

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ABSTRACT

The immune system distinctively has predominant concern of qualitative homeostasis. It serves housekeeper role for factors (majority of them, have endogenous origin) appearing as dangers for homeodynamics of the organism. Precisely, the immune system endeavors in dynamic optimal self maintenance within an organism which constantly faces varied infringements from the environment. Processes of growth, development and aging are all under supervision of immune system. The brain beholds perceptive topographic map of body architecture to both sense and issue actions in specified direction. The immune cells also behold broad image of the whole immunological self. By referring to this, the cells notice a danger molecule which is structurally non-conforming. This map is integrated with the antibody forming system or response forming system of these cells. Ability of immune system to detect unwelcome entries and then alert its various cell groups as well as the brain puts it at par with sensory organ. Classical features include active interactions with hypothalmo-pituitory-adrenal axis (HPA) or with autonomic nervous system mediated through specific peripheral and central cytokines. Immune system is committed to preservation of self by neutralizing dangers and keeps constancy and integrity of the organism. Immune response is evoked for restoring homeostasis consequent to damage. Secondly, interactions between activating and inhibiting mechanism of immune response needs to be optimally balanced.

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INTRODUCTION

Homeostasis in physiology refers much to quantitative balance. The immune system has distinctive concern of qualitative homeostasis. It serves housekeeper for largely endogenous factors perceived as dangerous for homeodynamics of the organism Amidst contradictory cells and molecules gaining entry into the organism harmonization of self has been indispensable for evolution. Such a role play by immune system possibly, evolved the capability to mount struggle against the non-self invaders as well [1]. Immune system carries out self maintenance, repairs, construction and optimization dynamically within an organism in face of varied infringements from environment [2]. A potentially dangerous molecule, including foreign molecules are identified and blocked. The system exhibits tolerance to commensale microbes and the fetus. The evolutionary tolerogenic adaptation of immune system as well as the stated objects is thus evident [3]. The immune system is disarmed against such foreign cells. The incompetent struggle mounted by the immune system to discard these entities, results in awakening of more of the genes and synthesis of products. The later that impart wider capabilities, particularly of repair and regeneration to meet higher rates of wear and tear during pregnancy and confinement.

Processes of growth, development and aging are all under supervision of immune system. Immune system has necessary ability to read genetic information in target cells to respond to them appropriately. This is facilitated by

free dissipation of cells. In contrast, neurons and endocrine cells that release neurotransmitters and hormones are not mobile. Mobile immune cells may reach their targets and inspect them through close contact.

Distinction between molecules is necessary for regulatory processes. The brain beholds perceptive topographic map of body architecture. Such map enables to sense exigencies and direct appropriate response. Immune cells also behold broad immunological image or map of self for reference to distinguish a nonconforming danger molecule. This map is integrated with the antibody and other response forming cells of immune system.

Danger recognition by immune cells is influenced also by receptors for hormones, autacoids, neurotransmitters, on these cells. Immune system on the other hand has potential to form auto antibodies against such regulatory molecules and their receptors. Immune system can therefore regulate respective functions along regulation by those molecules, viz, cell proliferation, differentiation, apoptosis (programmed death) and such genetically controlled molecular and cellular processes [4]. Auto-antibodies or anti-idiotypes exhibiting similar or opposite biological activities as those of hormones, autacoids, enzymes and drugs are well demonstrated in sick as well as healthy people [5].

Above scenario raises possibility that immune system may transgress the functional domains served by different specialized regulatory systems in body. The phenomenon on the other hand offers possibility of using anti-idiotypes for correcting genetic absence of some functional biomolecules. Anti-idiotypes to constituent bio-molecules normally formed in "physiological quantities" in healthy people may be harvested and administered in individual genetically deficient in concerned biomolecules. That should provoke immune response and generation of specific antibodies to the foreign anti-idiotype. There is good possibility of such antibodies being structurally similar to missing bio-molecules and may even function like them.

Early prenatal and postnatal patterning of Immune System

Environmental factors like malnutrition, stress or toxins affecting maternal immune system may disrupt development of fetal immune system. Interactions of maternal immune cells in decidua with trophoblast antigens and regulatory influence of immune cytokines, ensures tolerance to fetal/placental antigens by mother's immune system. The arrangements critically serve maintenance of pregnancy, development of fetal immune system and the competence of maternal immune system itself. Maternal and infant nutritional inadequacies can modulate the development of immune function [6]. The immunologic and regulatory framework in offspring can be permanently altered, determining risks for later disease [7]. Nutrition is basic need for organogenesis, normal proliferation of cells and synthesis of secretary products including cytokines, acute phase protein etc. The later is also essential to development of immune response machinery. Some nutrients are specifically needed for induction of control mechanisms in immune response e.g. antioxidants [8]. Nutrient deficiencies of mother compromise proper morphogenesis of placenta and restrict nutrient supply of fetus with profound global consequences to developing anatomy and physiology. The genetic programming also gets impacted [6, 9].

Food antigens in infant influence development of immune function through complex interactions with microbial flora of gut [10, 11]. Optimal oral tolerance to dietary constituents takes place early in 4 to 6 postnatal months. Failures of the same leads to food allergies, celiac and other inflammatory gut diseases [12]. There is critical involvement of many micronutrients in normal developmental processes of diverse capabilities of immune system. Nutrient factors related to single carbon metabolism, choline, folate (critically needed for DNA methylation) and Vit. $B_{2,}$ $B_{6,}$ and B_{12} are key modulators of epigenetic priming [6, 13]. Defective epigenetic priming of immune systems is linked to risk of allergic disorders [14]. Very important role in lymphocyte proliferation and differentiation, i.e. formation of regulatory T lymphocytes is ascribed to various fat soluble vitamins, viz. D, A, and E [15, 17]. Elemental zinc also has important role in lymphopoiesis and haematopoiesis.

The developing fetal metabolizing systems are vulnerable to toxic substances in mother's food (e.g. pesticides) which cross over to fetus and infant through placenta and breast milk. These may be detrimental to the immune function. Postnatal feeds influence the gut micro biota which interacts with gut mucosa to induce tolerance for commensales and ability to recognize pathogens. Humoral players of these interactions also influence the important central regulatory mechanism of immune responses namely, the hypothalamo-pituitary-adrenal axis. Malnutrition causes activation of the HPA axis and consequent suppressed immune function [18]. The permanent alterations in patterns of neuroendocrine-immune interaction lead to attenuation of inflammatory responses or reduced resistance to nidation and colonization of any tumor cells.

Maternal stress consequent to infection and inflammation involves increased expression of proinflammatory cytokines that are transmitted through placenta and breast milk for foetus/infants. Malnutrition partly determines quality (kind), quantity as well as transport of these mediators. Both a deficit of required nutrient/s or excess of

nutrients adversely impact immune functions. Cytokines would elevate HPA axis activity in fetus or infants, to increase glucocorticosteroid hormone levels. This has immunosuppressive effect, predominantly on the cell mediated Th1 type immune response. There is a shift toward the Th2 type immune responses and predisposition to allergic disorders [14, 19, 20]. Mental stress in mother also heightens HPA axis sensitivity in fetus. Normal gut flora that helps maturation of proper immune response, may be distorted by early antibiotic exposures. This may also shift immune response toward Th2 dominance, increasing risk of allergies and asthma [11, 21].

Functional scheme and regulation of immune system

The basic physiology limited to immune system itself may be narrated in idiotype-anti idiotype concept of antibodies and immune response. Immune system may be akin to a sensory organ given the ability to detect unwelcome entries and then alert its various cell groups as well as the brain. Immune system physiology essentially comprises understanding interactions of its constituents with other physiological systems. As a classical physiological system it actively interacts with hypothalmo-pituitory-adrenal axis (HPA) [14], or with sympathetic nervous system (even parasympathetic nervous system) [22, 23]. These interactions are mediated through specific peripheral and central cytokines. Immune system is physiological homeostatic system committed to preservation of self by neutralizing dangers and maintaining constancy and integrity of the organism. Immune function is unique in simultaneous and intertwined operation of physiological as well as pathological processes [24]. Different cells and mediators are put into action at different stages of the innate and adaptive immune responses. Precise synchronous changes in neural and endocrine activities provide its essential extrinsic regulation independent of consequences of stress or pathological state.

Interaction with antigen activates the immune cells to produce and release cytokines. The cytokines activate HPA axis leading to increased glucocorticosteroid secretion. The hormone suppresses incompletely activated or un-involved immune cells, but does not affect cells actively engaged in immune response [14]. Immune response is thus restricted to genuine requirement with enhanced specificity. This mechanism averts emergence of autoimmunity and excess proliferation in organs of the immune system.

The peripheral immune mechanism and endocrine responses under control of brain represent the long loop of regulatory circuit. Sympathetic nerves make close contact with immune cells in innervated lymphoid organs exerting inhibitory control. The later control is relaxed during active immune response. This is local short regulatory loop of neuro-humoral immune regulation [14].

Immune system reacts to antigen by informing the brain through variety of cytokines which also stimulate the HPA axis and inhibit nor-adrenaline turnover in hypothalamus besides some other hormonal effects [25]. Stimulation of β-2 adrenocepters by adrenaline and nor-adrenaline on the immune cells damps down release of pro-inflammatory cytokine. These effects occur on the antigen presenting macrophages and the effector Th-1 lymphocytes. In contrast the Th-2 lymphocytes get stimulated to liberate anti-inflammatory cytokines. Catecholamines therefore selectively suppress the inflammation and cellular immune response effected by Th-1 cells [26]. Both, catecholaminergic and serotonergic systems are dominant in integral control of immune function by brain [26, 27].

Cytokines interleukin IL-1 causes HPA axis activation through catecholaminergic mechanisms. Other neurophysiologic effects caused by cytokines are pyrexia, changes in appetite, sleep pattern, learning and memory. Both a direct impact on neurons through vasoendothelial-glial interface and by way of afferent vagus nerve impulses are involved in cytokine action [28, 29]. Humoral and neurotransmitter links of peripheral immune activity may induce expression of specific genes for cytokines and their receptors in specific regions of brain [30, 31]. Such signaling affects immune mechanisms in coherence to homeostatic adjustments in pathological state. Sympathetic activity causes circulatory enhancement facilitating passage of immune cells to conflict site. From the blood vessels and lymphatics these cells migrate and establish at site of action. The process is guided and controlled by adhesion molecules, chemokines, integrins and local factors [32]. Splenic link with circulation allows clearance, uptake and retention of microbes and their contact with immune cells. Systemically the cytokines increase sympathetic activity but high cytokine concentrations at action site inhibit neuronal nor-epinephrine release. Such strategic effect redistributes peripheral blood flow to flush the sites [33]. This enhances contact of antigen with immune cells necessary for mounting the immune response. Interleukin-1 exhibits strong potential of promoting glucose transport and oxidation in adipose tissue and fibroblasts. It also influences control of brain glucose utilization [34]. The peripheral and central IL-1 actions collectively channel glucose availability in lymphoid organs and inflammation site to sustain high energy needs of active immune response.

Inflammatory and autoimmune phenomena are crucially controlled by the immune-HPA circuit. Dysfunction of the circuit associates autoimmune inflammatory disorders [14, 35]. Auto-immunity is suppressed also by sympathetic nervous activity which promotes apoptosis in activated effectors lymphocytes during immune response [36]. Parasympathetic activation through the nicotinic receptor mechanism inhibits release of pro-inflammatory cytokines limiting the inflammatory process [37]. Catecholaminergic system co-localizes with specific neuro-peptide that exhibit pro or anti-inflammatory consequences in animal models of auto-immunity and modulate HPA axis function [38].

Cytokines produced in healthy brain play role in neurophysiology [31]. Their influence on neuro-endocrine control of homeostatic set points is vital immune-physiologic function. Antigen presenting cells are present in all organs and are influenced by hormonal and neurotransmitter mechanisms [8]. Most pathological states comprise of an inflammatory immune component that interacts with neuro-endocrine mechanisms. The demarcation between physiological and pathological is subject to decoding of the finite message carried by molecular mediators. The message depends on variety of states of time and site of microenvironment as well as the specific target.

The essential scavenging function

Immune function serves elimination of intruding microbes and immune complexes. This ability has evolved from extension of debris (of dying cells) removing function of immune system. Macrophages express Toll like receptor (recognizing non-self molecular patterns) and scavenger receptors (recognizing modified-self and alien protein structural patterns) for clearing endogenous and exogenous unwelcome products [39]. Intact cells (self or alien and old or young) and molecules (useful or waste) are not sensed by these cells. Only when auto-antibodies attach a target, it is signified for removal to the macrophages. The macrophages then bind by their membrane-born F_c-receptors to such targets (the soluble or particulate antigen-antibody complexes) and endocytose them for breakdown and elimination. The referred auto-antibodies are known as opsonins. Their guidance to macrophages is like that of scent, which enables dogs to recognize suspect objects. The quantity of processed antigen made available for recognition of immune competent cells, serves as regulator by positive feedback to the production of antibodies. This helps to maintain steady individual rates of apoptosis/replacement of specialized cells in healthy state. The different auto-antibodies also remain within defined 'physiological levels', not varying with age or sex [40]. Level of such organo-tropic auto-antibodies increases upon target organ pathology with increased cellular apoptosis releasing organ specific antigens. Such organotropic auto-antibodies therefore serve as biomarkers for specific organ pathology.

The Feto-Maternal harmonization and tolerance

Phylogeny and fetal development constitute essential physiology involving autoimmune harmonization. Fetal cells enter in to maternal circulation and this microchimerism is high in women bearing many pregnancies. The maternal immune system certainly attempts to mount immune response against the fetal cells but that is cut down to so called 'physiological' level. Partial elimination of invading fetal cells does occur without eruption of auto-immune disorder. The phenomenon is a defensive mechanism for sustaining pregnancy [41, 42]. The fetal cells are able to proliferate in mother due to physiologic regulation of auto-immunity and provide for repair and regeneration of damaged maternal tissues with fetal stem cells. In long run the subdued biological tussle envigourates maternal system serving as one basis of longevity of women [43]. The same may also contribute to higher incidence of auto-immune diseases in the female [44].

During the first trimester of pregnancy, decidual natural killer cells (dNK) localize in decidua, which facilitate trophoblastic invasion and growth of placental blood vessels. Interaction of dNK cells with trophoblast cells occurs through two kinds of receptors. A killer type and killer-inhibitory type receptors (KIR). The KIRs recognize Major Histo Compatibility Complex class-1 (MHC-1) present on nucleated cells.KIR signals dominate dNK cell behavior. Abnormal or damaged fetal cells lacking proper MHC-1 tag are destroyed [45]. The cytotoxicity of dNK cells is suppressed and trophoblast cells are spared of maternal immune attack. Such suppression results from strong activation of KIRs by interleukin IL-10, the class 1b (HLA E or G) molecules and class 1a alleles of HLA-C2 [46, 47].

An immune-depressant micro-environment is generated by cytokine IL-10 secreted by M2 sub-phenotype derived from the decidual macrophages [48]. Treg cells dominate the suppressor Treg/inducer T_{17} lymphocytes balance during pregnancy which is major determinant of maternal immune tolerance to fetus [49]. The Treg lymphocyte suppressor function begins even before fertilization to guard paternal antigens in insemination fluid [50].

Immune auto-reactivity and Auto-immunity

Sometimes a normal immune response may be feeble, less specific and badly driven. Perpetuation of the same would be detrimental to organism. Macrophage recognition and elimination of apoptotic debris is diminished in connective tissue disorders as systemic lupus erythematosus [51, 52]. Piled up apoptotic material is likely to be picked up for antigen processing and consequent signaling of auto-reactive lymphocytes. The auto-reactive process then exceeds ordinary or physiological limits. Even then this helps speedy clearing of aberrant cells restoring healthy organ function. The auto-antibodies stimulate repair function such as increased DNA synthesis, mitotic rate and cell proliferation [5, 53]. Raised auto-antibody level above the physiological limits indicate increased rate of apoptosis. This occurs much before dysfunction of organ detected in biochemical abnormalities and clinical manifestation. Organ non-specific auto-antibodies are also elevated years before occurrence of autoimmune disorders [54]. An autoimmune response (excess of the need to clear apoptotic matter) is mostly consequent to poor regulation.

Autoimmunity is kind of an adaptive secondary immune response. It is aberrant since it is not conditioned to serve need of the organism. Hereditary predilections to autoimmune diseases point to genetic aberrations and/or epigenetic changes resulting from environmental factors. These crucially alter the magnitude/intensity of immune response [55-57]. Unique change in bio-molecular structure amid pathologic states [58], or mimicry of nucleic acid products to those of infective microbes in damaged cells [59] may make them appear as alien antigens to the immune cells to mount autoimmune response. Encounter of immune cells with such immunogenic substances may increase also with failure of cellular organelles to capture and check such molecules [57]. Adverse environments cause epigenetic changes and stress in the host may cause hypo or hyperactive neuro-endocrine functions [23].These would tilt immune responses toward Th-1 or Th-2 over-activity patterns [60]. Thus, internal and external aberrations on varied accounts may promote and erupt autoimmunity [61].

Epilogue

The immune response is evoked to restore homeostasis upon encountering external intruders or endogenous products of tissue damage. Synergic balanced interactions between activating and inhibiting mechanism of immune response ensure defense and avoid severe immune pathologies. The differences of molecular mechanisms involved in sensing danger from the self derived versus foreign entities needs finite understanding as prerequisite to understand autoimmunity [23]. The apparent contradiction in rejection of transplants but not pregnancy by the immune system has resolved with such understanding. Immune system seems cognizant of disturbances in milieu and decides about using only innate or also adaptive kind of responses. The later is based on overall sensory and referent integration.

The normal physiology of T and B lymphocytes includes weak self-reactivity. That serves maturation and diversity of immune potential. That also regulates cell survival to the optimum span for integrity of function and health. Immune system is fundamentally tuned to serve physiological role and naturally acquires learning toward stepping in to war against unwelcome molecules and cells. The academic tradition prevailing for more than a century, has largely denied basic and applied physiological view of the immune system. This article emphasizes such view beyond the realm dominated by the 'foreign' and the 'abnormal'. Such a view ought be useful for holistic understanding of immune system.

Authors' Contributions

All authors contributed equally to this work.

Competing interests

The authors declare that they have no competing interests.

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