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Dysfunctional Lymphocyte Turnover in Subsequent Self-Generation of Autoimmunity

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Abstract: Reactivity responses of autoimmune origin appear a realized series of pathways in the generation of dysfunctional versus homeostatic lymphocyte turnover. Lymphocyte responsiveness would transform to a dysfunctional state in the generation of various subsets of cells as reflected in autoimmune phenomena. It is in terms of a dysfunctionality ranging in scope from primary generation of the lymphocyte subset to subsequent creation of a whole panorama of responsive influences and pathologic lesions that autoimmunity would evolve further as a self-generated reactivity in its own right. Indeed, oligoclonality of antibody production in the cerebrospinal fluid of multiple sclerosis patients would arise as a phenomenon both primarily generated in terms of dysfunctional lymphocyte turnover and as a secondary process in the progression of such primary autoimmune reactivity exposing native myelin epitopes.

Key words: Self genration,auoimmunity, dysfuntional, lymphocyte

INTRODUCTION

AUTOIMMUNITY-"DECYCLING" OF IMMUNE SUBSET CELLS OR OF IMMUNE REACTIVITY?

A central problem relative to a specific conceptual mechanism of autoimmunity as pathogenetically responsible for an overprogressiveness in evolution of a number of disease processes affecting individual organs is understanding what triggers such autoimmune response. T lymphocytes are involved in control of infection and also in prevention of inflammation and autoimmune disease[1]. In this sense, perhaps, one might view autoimmunity as a derangement of essential cycling of lymphocytes and other immune cells that relate particularly to systems of cellular homeostatic turnover. The Fas-Fas-L system regulates cytotoxic activity of lymphocytes and is activated by hyperthermia. This enhances transcriptional activity of AP-1 and NK-kappa in activated T cells. Modulation of PKC activity may also be important in this regulation[2]. Indeed, perhaps, one might, for example, view oligoclonal antibody production in the cerebrospinal fluid of patients with multiple sclerosis as suggestive of a predominant-target cell determinant role in such autoimmunity, involving T -cell epitope specificity[3]. In a sense, autoimmune response might constitute a nonspecific phenomenon that is conditioned by specific target -cell types contextually evolving as cellular decycling events.

Transcriptional dependence on ATP generation and on glycolytic genes, a dual role of chromatin reorganizing genes in transcriptonal activation and repression and G-protein-mediated signals in target gene expression appear critical in lymphocyte homeostasis[4].

Lymphocytes and associated immune cells may include members of the innate to adaptive systems as primarily cycling events implicating a full series of transformations ranging from reactivity to proliferative, differentiating and self-renewal survival mechanisms. There may be impaired lymphocyte response to Interleukin-7 as evidenced by in vitro proliferation and secretion of interferon gamma and transforming growth factor beta[5]. Additional mechanisms such as viral proteases possibly generate novel protein fragments by targeting "immunocryptic" autoantigen[6]. Apoptosis of lymphocytes, such as seen affecting CD8 + T cells, may indicate lymphocyte dysregulation and imbalance [7].

Aberrant cyclical activity of lymphoid cells may involve a core phenomenon of disorders arising and progressing within frameworks of reactivity to native body tissues. Interleukin 21 costimulates proliferation of T lymphocytes, modulates homeostasis and enhances memory response; it is also involved in terminal differentiation of Natural Killer cells[8].

IL-21 receptor is expressed on T, B and NK cells; IL-21 regulates IgG1 production in B cells and is involved in terminal differentiation and maturation of B lymphocytes[9].

The nature of the response in organ-specific autoimmunity would appear to critically implicate a disease-inducing antigen[10]. B and T lymphocyte

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attenuator (BTLA) provides an inhibitory signal to B and T cells and interactions with herpes virus entry mediator may regulate lymphocyte activation and homeostasis of immune response[11]. The lymphocyte pore-forming protein perforin is particularly effective against intracellular pathogens and also for maintaining immune homeostasis[12].

However, even if one were to consider multiple sclerosis or systemic lupus erythematosus or dermatomyositis as simply systemic disease responses to specific tissues or organs, in a broader sense, perhaps, accompanying systemic involvement would progress as consequential patterns of autoimmune responsiveness. Cytokines and signal transducers and activators of transcription (Stat) and Janus tyrosine kinases (Jak) in particular regulate a critical balance between homeostasis and apoptosis of T- and B- lymphocytes[13].

In overall terms, perhaps, native tissues are active participants of systemic progressiveness involving activation of various pathways such as Toll-like receptivity relative to innate immunity; also, various multiple mechanisms of injury to cells would be sustained in times of active "decycling" of immune reactivity. Naïve B and T lymphocytes utilize CXCR5/CXCL13 for migration, homing, maturation and cell homeostasis; apoptosis and cell-cell contact and cell proliferation may be modulated by CXCR5 in CD8 (+) CD34 (+) T cells[14].

It is, indeed, in terms of an essential cycling series of activities as primary attributes of immune response that immune cellular biologic systems of influence would induce pathways of cellular and tissue damage. Multiple heterogeneous factors of etiopathogenesis in patterned disease progressiveness would range from demyelinative to vasculitic to systemic disturbance of, often, fluctuating severity, clinically and pathologically. Abnormal T cell activation and cell death underlie the pathology of systemic lupus erythematosus, involving mitochondrial hyperpolarization as mediated by nitric oxide[15].

In this way, serum Dnase1 together with the plasminogen system would effectively breakdown chromatin during necrosis and subsequently lead to antinuclear autoimmunity in systemic lupus erythematosus[16].

These patients who show different aspects of disturbed B cell homeostasis such as low CD21 levels[17].

With regard to multiple sclerosis, the typical remitting/relapsing clinical course of neurological dysfunction might arise as systems of progressive derangement superimposed on previously established baselines of mounting disturbance affecting myelin synthesis and deposition around axons. In such a context, activation of autoreactive T cells is centrally implicated in an autoimmune response implicating such mechanisms as T-cell receptor degeneracy and molecular mimicry[18]. During massive inflammatory responses, CD4+CD25+ Tregs suppress priming and/or expansion of polyclonal autoreactive responses nonspecifically. Otherwise, TCR-specific negative feedback mechanisms achieve a fine homeostatic balance[19]. B lymphocyte stimulator (B cell activating factor) of the Tumor Necrosis Factor family and proliferation inducing ligand binds to B cell maturation antigen, B cell activating factor receptor and transmembrane activator and CAML interactor. These appear implicated particularly in B cell autoimmunity via maintenance and survival mechanisms[20,21].

A system of demyelination would relapse and remit in terms of an apparent cyclical turnover of systems of progression affecting primarily the oligodendrocyte.

Indeed, one might even relate demyelination of multiple sclerosis plaques not only to decycling of regional groups of oligodendrocytes but particularly to groups that predetermine decycling attributes within integral frameworks of overall progression of the multiple sclerosis process in that particular patient.

Even insofar as vascular distribution relating to plaque localization is concerned, the relapsing/remitting course of multiple sclerosis is not primarily determined by an etiologic factor of fluctuating type but by a cyclical progression in severity that implicates clonal subsets of immune cells.

In this regard, HLA Class I and Class II molecules are critical in antigenic peptide presentation to T cells, in a way that initiates adaptive cellular and humoral immune responses[22]. In homeostatic proliferation, naïve T cells proliferate in response to self MHC molecules after transfer into lymphopenic hosts; this is mediated by interactions with the same MHC molecules responsible for positive selection in the thymus[23].

Clonal proliferation of immune cells includes T lymphocytes and also members of the innate immune system such as macrophages that arise due to decycling of cellular homeostatic turnover.

Cross talk may occur between human CD4 + T cells and NK receptor-activated NK cells via OX40-OX40 ligand interactions[24]. Mantle zone B lymphocytes bridge the gap between innate and adaptive immunity as exerted by follicular B lymphocytes and may be involved in homeostasis and tolerance[25].

It is in terms of a deranged cyclical pattern of lymphocytes and other types of immune competent cells that macrophages would incorporate injury to myelin within the additional contextual involvement of the

oligodendrocytes inducing demyelination in multiple sclerosis.

It is in terms of a primarily cyclical cellular turnover that a homeostatic system would predetermine both cell survival and differentiation pathways. Fas, a TNF receptor superfamily member, mediates apoptosis of lymphocytes via FADD and caspase 8. Surface receptor oligomers consequently form and these may be disrupted in cases of Fas mutations from patients with autoimmune lymphoproliferation[26].

At the cellular level, autoantigens in general, in addition, become clustered as surface blebs of apoptotic cells, leading subsequently to changes in molecular structure of epitopes during development and homeostasis[27].

One might view multiple sclerosis as an expressive autoimmunity selectively determined by various perturbations or derangements of such cyclical turnover of T and also of B lymphocytes and macrophages.

T cell receptor integrity functions in both antigen recognition and signal transduction and is vital for an optimal immune response[28].

A single system of progressiveness would arise as generated patterns of decyclical activity that in various ways distort immune reactivity. Leukocyte membrane receptors for the Fc portion of immunoglobuins link antigen recognition by antibodies to effector immune function involving also autoimmunity[29]. In this way, for example, inflammatory caspases such as caspase-1 and caspase-5, would appear implicated in dysregulatory inflammatory responses beyond simple considerations of just apoptotic cell death[30]. Cytokine-induced SOCS family adaptors function as feedback inhibitors of cytokine receptor signaling by inhibiting the JAK-STAT signal transduction pathway[31].

An integral cellular determination of such cyclical activity in terms particularly of immune reactivity would reflect loss of oligodendrocyte viability as a constitutive decyclical event in multiple sclerosis.

Such events may develop as periodic breakdown of myelin in an apparently global process of meningoencephalitis.

This would manifest itself as multiple, randomly distributed demyelinative plaques in the CNS that implicate oligodendrocyte primary determinants of a progressive decycling nature developing along etiopathogenic pathways of progressive auto-immune reactivity.

IS AUTOIMMUNITY A LYMPHOCYTIC RESPONSE OF STRICTLY FAILED HOMEOSTATIC TURNOVER?

A system of cyclical turnover might possibly constitute active homeostatic control relating to both lymphocyte differentiation and lineage progression. Study of lymphocyte trafficking may reveal critical aspects of immunity and of T lymphocyte homeostasis in disease by defining immune dysfunction in continuous surveillance pathways[32,33]. A concept of such dimensions might indeed help account for the evolution of pathologic effects that arise as a progressive reactivity of lymphocytes and other immune competent cells against many different native cell types. Type I Interferons (IFN-alphabeta) enhance immune responses, notably proliferation and survival of naïve CD4 + T cells during primary response[34]. In addition, a "two-hit" signal composed of autoantigens and adjuvants may initiate systemic autoimmunity as exemplified by systemic lupus erythematosus[35].

Even in terms that would account for a disease process depending on cellular and tissue injury, in a strict context of primarily organ damage, one might perhaps recognize autoimmunity as a primarily defective cyclical turnover in homeostatic lymphocyte functionality. This would evolve as defective lymphocytic differentiation.

IL-15 promotes the proliferation of memory CD8 + T cells. IL-2 suppresses their division in vivo, apparently in an indirect fashion via other cell populations such as CD25 + CD4 + T cells[36].

Dynamic systems driven by opposing vectors Interferon-alpha/beta and Tumor Necrosis Factor have been proposed to differentially activate dendritic cells; dysregulation of such activation may possibly be implicated in generation of the autoimmune response[37].

According to such evolving autoimmune responsiveness that allows and also actively induces organ damage, various cells and tissues of a region or organ would develop specifically as evolving pathophysiologic lesions.

In this sense, autoimmunity of a primarily pathologic nature would implicate evolving change primarily involving loss of homeostatic turnover of lymphocytes, particularly affecting links between inflammation and autoimmunity[38]. Lineage evolution and modes of lymphocyte differentiation would constitute a full constellation of involved phenomena linked inherently to a lymphocyte dysfunctionality and to an abnormal range of immune reactivity. Galectins may immunoregulate T cell homeostasis and sensitize them to Fas (CD95)/caspase-8 mediated cell death and thus influence response to chronic inflammation[39].

In terms, therefore, that would help account for a lack of triggering mechanisms in the initiation and sustainment of autoimmunity both as a response and especially as a cellular and tissue injury, there would evolve various pathways of potential lesion infliction.

These would constitute a deterioration of functional receptivity reactivity of various lymphocyte lineage subsets in terms of negative T cell costimulatory pathways[10].

Indeed, such lymphocyte lineage subsets that one might include an autoimmune response as a degradation affecting self-progression. This would operate on a basis of an antigenicity that evolves as an exposure phenomenon of molecular-domain type. Defective negative selection in the thymus together with positive selection of immature double-positive thymocytes possibly result in differentially evolving lineages of lymphocytes including autoimmune reactive clones[40].

Autoimmunity might be strictly interpreted as a cellular rejection phenomenon effected by systems of humoral antibody response that evolve within a contextual framework of ongoing tissue and cellular injury. Autoimmunity in chronic graft-versus-host disease possibly depends on failure of B-cell tolerance at multiple checkpoints[41].

In this way, evolving cellular membranous injury and receptor-mediated cascade events would incorporate cellular dysfunctional states that are either lytic in terms of precipitation or else progressive.

Homeostatic turnover of lymphocyte lineage subsets might implicate sustained initiation and termination of functional differentiation pathways that relate to reactive patterns of antibody response and antigenicity. Natural Killer cells may suppress or enhance immunity by promoting the secretion of Th1, Th2 or immune regulatory cytokines[42] and are potent activators of dendritic cells. Viral infection may affect magnitude and direction of dendritic cell activation of T cells[43].

Such a fundamental paradox might refer to a reactivity of B and T lymphocytes arising and sustained largely as essential lymphocyte lineage derivation and evolution.

BEYOND SELECTIVITY OF AUTOIMMUNITY AND OF AUTOIMMUNE REACTIVITY AND RESPONSE

A concept of autoimmune reactivity that implicates pathways of lesion generation affecting central nervous system, endocrine organs, connective tissue, joints and skeletal muscle might effectively involve the creation of cellular and humoral responsiveness largely centered on macrophage-mediated phenomena.

Even in the case of multiple sclerosis that involves a T-cell response as reflected also in the Experimental Allergic Encephalomyelitis model there would be implicated macrophages as full participants of the core disease process of autoimmune progression.

Macrophages would constitute modalities of phagocytosis somehow inherent to systems of cytokine-mediated events starting and propagated in a full setting of secondary and tertiary order events and as subsequent tissue lesions.

Also, a failed anti-T-cell-receptor response by T cells may possibly lead to an immune dysregulation effecting the onset of a pathogenic autoimmune response[44]. Follicular dendritic cells in particular appear to directly affect germinal center T cell migration within lymphoid follicles[45]. Dendritic cells are the most potent of antigen-presenting cells, especially to naïve T lymphocytes[46].

Indeed, for example, the Graves disease model of autoimmunity would specifically relate to a follicular hyperplasia that does not parallel in severity the thyrotoxic state. It is in this sense perhaps that cellular release phenomena as referable to thyroid hormones would evolve as a reactivity consequent to a receptor-mediated series of effects and consequences.

Germinal centers prominently characterize many of the lymphoid follicles in the thyroid affected by Graves' disease.

In addition, the Hashimoto thyroid model of autoimmune response would specifically involve a highly specific organ phenomenon reflected paradoxically in a generalized autoimmune state.

Such a generalized state of autoimmunity that is organ specific even in terms of manifested tissue injury would help account for the initiation of disease progression affecting a primarily homeostatic triggering of the autoimmune reactivity.

Interferon gamma is produced especially by CD8 + T cells, in response to antigen presenting cells with few peptide ligands consistent with an early immunoregulatory role of CD8 + T cells[47].

In this sense, for example, myasthenia gravis, as a paraneoplasia involving a state of autoimmunity that is initiated and sustained within specificities of the thymus and of the neuromuscular junction, might actually incorporate a site of autoimmune attack. This would be primarily selected as localized events implicating reactivity rather than selectivity.

A strict distinction of cycling events regarding homeostatic control of lymphocyte lineage subsets might implicate especially a macrophage participation affecting genesis and subsequent development of antigenicity and of antigenic epitopes involving neuromuscular junctions.

In general, defective homeostatic proliferation of T cells, after selective T cell depletion in disease, might possibly promote the autoimmune response in such cases[48]. Also, NK cells can migrate throughout the body in an unprimed state and increase specificity in homing to

sites of inflammation; it also recruits various immune cells to sites of immune response[49].

In a final analysis, autoimmunity may evolve as a reactivity that, far from being selective, is primarily a state of responsiveness arising and sustained as a primarily altered modulation of homeostatic versus dysfunctional cycling of constitutive lymphocyte turnover. In this regard, peripheral autoantigen-binding B cells are poorly competitive with naïve B cells and are rapidly eliminated. Otherwise, as with elevated BAFF levels, autoimmune disease may develop[50].

Both CTLA-4 and TGF-beta have been implicated in suppression by CD4 + CD25 + regulatory T cells (Treg). CTLA-4 regulates Treg function during functional development and also during the effector phase when the CTLA-4 signaling pathway is required for suppression[51].

IS PARANEOPLASIA A SPECIAL CASE OF THE AUTOIMMUNE STATUS?

Myasthenia gravis, far from being a dysequilibrium between idiotype and anti-idiotype reactivities, would perhaps effectively originate and progress as an ongoing epitope exposure that does not evolve simply as anti-cholinergic receptor damage, but rather as a system of promotion of impaired lymphocyte subset replacement. In this sense, in myasthenia gravis, replacement of specificity-directed reactive lymphocytes would primarily arise within a setting of thymocyte pathophysiology and dysfunction. The association, indeed, of anti-cholinergic receptor antibodies with thymus hyperplasia and thymoma would perhaps account for a disorder that mimics in various ways the Eaton-Lambert paraneoplastic state. This evolves primarily as an epigenesis of the proliferative progression of a small cell carcinoma of the bronchus.

In this sense, perhaps, paraneoplasia might constitute a component in genesis of a neoplastic proliferation related to turnover of lymphocyte subsets and to specific immune reactivity and response.

FAILED OR SUCCESSFUL GENERATION PATTERNS IN THE GENESIS OF THE AUTOIMMUNE STATUS

Evolving autoimmune reactivity perhaps conforms to strict patterns of cellular injury in a context not only of antigenic epitope exposure but also of mechanistic progression of such cellular injury. The selective up-regulation of caspase-3 transcription is required to maintain cytoplasmic levels of this protease, which control activation-induced cell death and T cell homeostasis[52]. In this sense, one might conceive of an immune reactivity that is dysfunctional beyond just membrane receptivity or antigen-antibody reactivity. IL-15 during priming selects or induces higher-avidity Cytotoxic T cells; these persist longer by homeostatic proliferation[53]. In a context of simple transfer systems of evolving influence that can and do progress, the autoimmune status might induce a reactivity that is not receptor-mediated nor primarily affecting either antibody reactivity or antigen exposure in its initial generation. It is possibly relevant to consider autoimmune responsiveness as an untoward exaggeration of the immune mechanism that biologically is not distinct from normal reactivity except in terms of its specificity[54].

In terms, perhaps, that would implicate a full series of failed systems of sustainment of newly evolving patterns of antigenic reactivity, one might simply view antibody-mediated and cellular immune responses as states of primary evolution based on either failed or successfully maintained macrophage response. These would act as modulators of pathway responsiveness that are subsequently translated into specific tissue organ injury. B-1 lymphocytes can downregulate the effector functions of macrophages via Interleukin 10 secretion, as related to zymozan particles and release of nitric oxide and hydrogen peroxide[55].

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