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SCIENCE DIRECT®
Molecular Immunology 42 (2005) 811–820
Molecular Immunology
www.elsevier.com/locate/molimm

Review

Hormonal modulation of B cell development and repertoire selection

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Received 24 March 2004; accepted 27 May 2004

Abstract

Systemic lupus erythematosus is an autoimmune disorder characterized by the production of pathogenic autoantibodies, primarily to nuclear antigens. The etiology of SLE is not entirely understood, but it is well-appreciated that multiple factors such as genetics and environment contribute to disease progression and pathogenesis. There is also convincing evidence that gender plays an import role in SLE since the incidence of disease occurs with a female to male ratio of 9:1. While it is plausible that some sex-linked genes may contribute to the genetic predisposition for the disease, other likely culprits for this gender bias are the sex hormones estrogen and prolactin. The data implicating estrogen and prolactin in SLE, until recently, were largely circumstantial. However, within the last few years, data collected from both human and mouse studies have provided compelling evidence that alterations in sex hormone levels can alter tolerance of autoreactive B cells and exacerbate disease. In this review, we will discuss recent data demonstrating a role for estrogen and prolactin in SLE and the effect of these hormones on B cell maturation, selection and activation.
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Keywords: B cell; Systemic lupus; Erythematosus; Autoantibody; Tolerance; Estrogen; Prolactin

1. Introduction

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease of the musculoskeletal system, which predominantly affects females (Ahmed et al., 1985; Grossman et al., 1991). The hallmark of SLE is the production of pathogenic autoantibodies specific for nuclear antigens such as ribonucleoproteins and chromatin (Davidson and Diamond, 2001). The deposition of these autoantibodies in target tissue such as the kidney, heart and brain can trigger an inflammatory response that causes organ damage. The factors that are involved in disease progression are complex, but it is clear that genetics, environment and gender all play a role. Much of our understanding of the molecular basis for human lupus comes from studies of mouse models of SLE. The New Zealand Black/New Zealand White (B/W) F1 and the MRL/lpr mouse strains develop lupus by 5 months of age and, similar to the human disease, exhibit high titers of antinuclear autoantibodies and develop glomerulonephritis (Bell et al., 1973; Pisetsky et al., 1980). Since these mice develop the disease spontaneously, the B/W F1 genetic background in particular has been used to dissect the genetic loci that contribute to SLE (Drake et al., 1994; Morel et al., 1994). Studies of environmental triggers have also yielded important information about SLE. Peptides that mimic self-antigens such as DNA (Putterman and Diamond, 1998) and Ro (Farris et al., 1999) and chemical agents such as mercury chloride (Pollard et al., 2001) can induce a lupus phenotype in certain mouse strains, indicating that environmental triggers may be a critical component of disease progression. Finally, similar to the human disease, some mouse models of lupus also exhibit a gender bias. Female B/W F1 mice exhibit an earlier onset of disease and a shorter life span (Roubinian et al., 1978). This phenotype is exacerbated by administration of 17 β-estradiol and improved by administration of testos-

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0161-5890/$ – see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.molimm.2004.05.014

terone (Roubinian et al., 1979). The gender bias observed in human lupus patients is also strongly supportive of a role of sex hormones in SLE (Ahmed et al., 1985; Grossman et al., 1991). This review will focus on what has been learned about the effects of administration of the sex hormones estrogen and prolactin on B cell tolerance and how elevations in either estrogen or prolactin may contribute to autoantibody production.

2. Overview of B cell development, selection and activation

Generating a repertoire of B cells capable of recognizing a diverse and broad array of microbial antigens and toxins is critical for an organism's survival. Yet, the diversity of antigenic recognition must be limited so as to avoid autoreactivity. B cell autoreactivity is dictated by the specificity of the antibody or immunoglobulin molecule. The immunoglobulin molecule consists of two identical heavy chain and two identical light chain molecules linked by disulfide bonds (Frazer and Capra, 1999; Janeway et al., 2001a). The variable regions of the heavy chain and light chain form the antigen binding site. The heavy chain variable region is encoded by gene segments termed the V, D and J genes (Early et al., 1980; Sakano et al., 1980) and the light chain is encoded by V and J genes (Bernard and Gough, 1980). The random recombination of these variable gene segments, coupled with the random association of heavy and light chain molecules gives rise to a diverse repertoire of different antibody molecules. Both non-autoreactive and autoreactive B cells arise normally during B cell repertoire development. When the immunoglobulin is expressed as a secreted molecule, it executes effector functions by the constant region, which vary for the μ, γ, α and ε constant region domains (Janeway et al., 2001b). When expressed as a cell surface molecule, it forms the major component of the B cell receptor (BCR), which also includes the molecules Igα and Igβ. The cytoplasmic tails of the Igα and Igβ transduces signals critical for BCR signaling events involved B cell development and activation (Clark et al., 1994). The BCR plays a critical role in the negative selection of autoreactive B cells (Healy and Goodnow, 1998; Sandel and Monroe, 1999).

The early stages of B cell development in adults occur in the bone marrow (Hardy et al., 1991). Pluripotent stem cells give rise to the first recognizable B cell stage, which is the pro-B cell stage. Heavy chain gene rearrangement, which is mediated by proteins encoded by the recombination activation genes RAG-1 and RAG-2 (Li et al., 1993; Oettinger et al., 1990), occurs at the pro-B cell stage. Expression of the heavy chain molecule is required for the continued maturation of pro-B cells into pre-B cells. During the late pre-B cell stage, light chain gene rearrangement takes place, also mediated by RAG-1 and RAG-2 (Li et al., 1993). Upon successful rearrangement of the light chain molecule, pre-B cells differentiate into immature B cells. Surface expression of the newly rearranged IgM molecule occurs at the immature B cell stage of development. Before becoming fully competent mature B cells, immature B cells develop into transitional B cells. The most immature transitional B cells are termed transitional type 1 B cells (Carsetti et al., 1995; Loder et al., 1999). These migrate to the spleen and give rise to the more mature transitional type 2 B cells. Mature B cells develop directly from the transitional type 2 population or possibly from cells recently described as transitional type 3 B cells (Allman et al., 2001).

Since autoreactive B cells are generated following the random rearrangement and association of heavy and light chains, there is a necessity to purge those cells. The mechanisms that regulate tolerance induction of autoreactive B cells have been extensively studied in mice that express transgene-encoded autoantibodies. Receptor editing, clonal deletion and anergy are all mechanisms used to select a repertoire of non-autoreactive immunocompetent cells. Receptor editing occurs in autoreactive cells at the immature B cell stage in the bone marrow following crosslinking of the BCR by self-antigen (Gay et al., 1993; Tiegs et al., 1993). At the genetic level, the light chain of a self-reactive antibody can be replaced by a new light chain, or less frequently the heavy chain by a new heavy chain, thus replacing the autoreactive specificity with a non-autoreactive one. This rescue has been correlated with the re-expression of RAG-1 and RAG-2 (Tiegs et al., 1993; Yu et al., 1999). There is evidence that the more immature IgM^{lo}/IgD^{lo} B cells are susceptible to receptor editing to achieve tolerization, while the more mature IgM^{hi}/IgD^{lo} B cells are regulated by clonal deletion (Melamed et al., 1998), suggesting that the stage of B cell development determines how B cells are tolerized. Clonal deletion is thought to occur when receptor editing fails, and is mediated by apoptosis of autoreactive B cells (Sandel and Monroe, 1999). If the engagement of the BCR by antigen is insufficient to trigger apoptosis, autoreactive B cells may migrate from the bone marrow to the spleen. These cells exist, however, in a state of non-responsiveness, which is termed anergy (Goodnow et al., 1988). These B cells fail to respond to antigen and T cell help, and display reduced expression of IgM. They will, however, respond to T cell-derived mediators such as CD40 ligand and IL-4, and thus, can be activated to secrete autoantibody under pro-inflammatory conditions (Cooke et al., 1994).

Immature B cells that escape negative selection move into the periphery where again, they may be subject to negative selection. Transitional B cells in the spleen that respond to self-antigen undergo clonal deletion or anergy (Carsetti et al., 1995; Sandel and Monroe, 1999). Whether transitional B cells undergo receptor editing has not been determined. B cells that mature to immunocompetence become either follicular or marginal zone B cells. These subsets reside in distinct anatomical locations and differ in their phenotype (Sagaert and De Wolf-Peeters, 2003). Follicular B cells, which are located in B cell follicles require antigen and helper T cells for activation. Marginal zone B cells, which are found pre-

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