

The aged immune system in multiple sclerosis: focus on B cells

Multiple sclerosis (MS) is an autoimmune disorder that affects the brain and spinal cord. A chronic inflammatory reaction causes breakdown of myelin surrounding the axons, leading to a disturbed transmission of nerve impulses. Symptoms of MS include muscle weakness, loss of sight, fatigue and walking difficulties. Magnetic resonance imaging (MRI) pictures of the brain show lesions containing immune cell infiltrates.

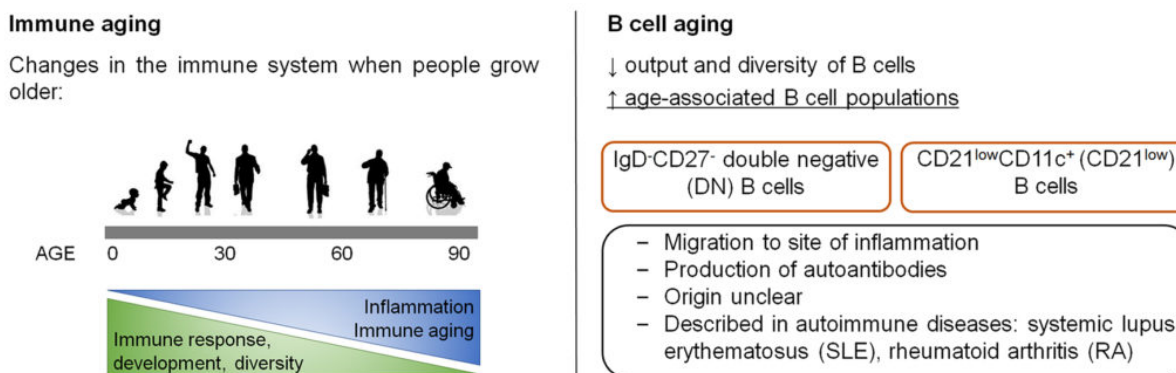


Fig. 1. Immune and B cell aging. During aging, the immune system undergoes changes (left) that lead to increased inflammation and decreased immune responses. One of the consequences of immune aging on the B cell compartment (right) is the accumulation of age-associated B cells such as double negative (DN) and CD21^{low} B cells. These B cell populations share several characteristics that render them interesting targets for further study in autoimmunity.

B cells are immune cells that belong to the lymphocyte population. They recognize and bind antigens using a specific receptor, become activated and undergo maturation into effector plasma cells that produce large amounts of antibodies. In MS, B cells are important players in the disease process. Plasma cells produce autoreactive antibodies (autoantibodies) but B cells also stimulate proinflammatory immune responses by presentation of specific antigens and providing costimulatory signals to other immune cells. In addition, B cells produce proinflammatory molecules, cytokines, that contribute to the detrimental immune response in MS.

During aging (Fig. 1), the immune system undergoes changes that lead to increased bacterial and viral infections while vaccine efficacy declines. Further, modifications of immune cell repertoires and functions are observed. Aging is linked to autoimmunity as autoimmune disorders occur more frequently in the elderly. Interestingly, a proportion of MS patients display characteristics of an aged immune system. B cell immunity is also affected by aging, as a decline in the output of new B cells leads to reduced protective antibody responses and increased generation of autoantibodies. Diversity in the antigen specificity of B cells and antibodies is reduced and specific populations of ‘age-associated B cells’ accumulate, such as the double negative (DN) immunoglobulin (Ig)D⁻CD27⁻ B cells and the CD21⁻CD11c⁺ (CD21^{low}) B cells. Both of these have been associated with the production of autoantibodies and are able to migrate towards sites of inflammation although their

origin remains unclear. DN and CD21^{low} B cells have been described in autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

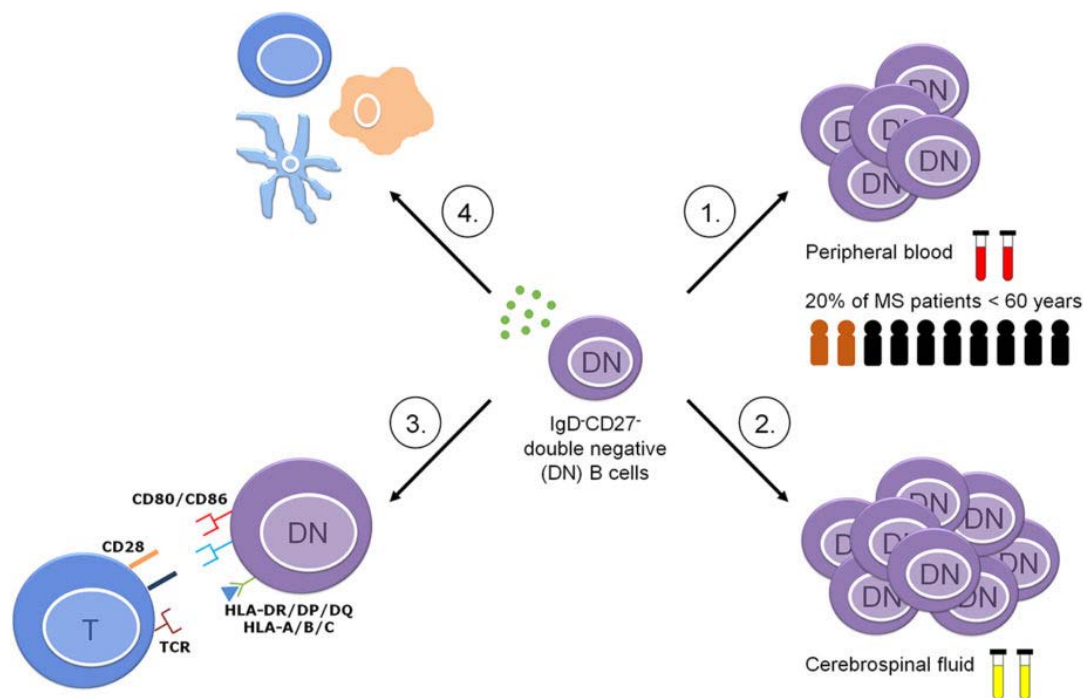


Fig. 2 Functional characteristics of DN B cells in MS. (1) DN B cells are expanded in the peripheral blood of 20% MS patients < 60 years. (2) Frequencies of DN B cells are increased in the cerebrospinal fluid of MS patients when compared with the peripheral blood. (3) DN B cells express molecules involved in antigen presentation (human leukocyte antigen (HLA)-DR/DP/DQ and HLA-A/B/C) and costimulation (CD80, CD86) to T cells, another immune cell population belonging to the lymphocytes. (4) DN B cells produce proinflammatory cytokines that stimulate other immune cells, such as dendritic cells, macrophages and T cells.

To examine whether DN and CD21^{low} B cells are involved in MS pathology, we performed a screening and functional study in MS patients. We first confirmed the association of DN and CD21^{low} B cells with aging, as we measured increased frequencies of these B cells in the peripheral blood of healthy donors > 60 years when compared with healthy donors < 60 years. Further, we analyzed individuals with frequencies of DN or CD21^{low} B cells above a predetermined threshold, indicating an expansion of these cells. We found an increased proportion of young MS patients (< 60 years) with expansions of DN B cells (20% of young MS patients) and CD21^{low} B cells (22% of young MS patients) when compared with young healthy donors (3% for DN B cells and 6% for CD21^{low} B cells). These results indicate a premature expansion of age-associated B cells in a proportion of MS patients. Frequencies of DN and CD21^{low} B cells were further elevated in the cerebrospinal fluid (CSF) of MS patients, a watery fluid that is present in the brain and spinal cord. Next, we performed a functional analysis of DN B cells and demonstrated that they could play a role in antigen presentation and proinflammatory functions. DN B cells of MS patients showed similar expression levels of antigen presentation molecules as memory B cells, a B cell subtype known to be

involved in MS pathology. In addition, DN B cells produced proinflammatory and cytotoxic (toxic to living cells) cytokines, pointing to their proinflammatory profile. Together, our results indicate the expansion of age-associated B cells in a proportion of MS patients that could contribute to MS pathology by proinflammatory functions (Fig. 2).

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Publication

[Age-Associated B Cells with Proinflammatory Characteristics Are Expanded in a Proportion of Multiple Sclerosis Patients.](#)

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