Premature Thymic Involution and Multiple Sclerosis

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Abstract

It is uncertain as to whether similar or different mechanisms contribute to different subtypes of multiple sclerosis (MS). A unifying concept proposes that patients with both relapsing-remitting MS (RRMS) and primary progressive MS (PPMS) have premature thymic involution, which alters peripheral T-cell homeostasis and leads to T-cell alterations that contribute to the pathogenesis of both MS subtypes.

Commentary

Multiple sclerosis is a complex, heterogeneous disorder of the CNS. An unresolved issue is whether similar or different mechanisms contribute to the different MS subtypes. Most think that peripheral immune mechanisms contribute to attacks in RRMS but not in PPMS [1]. An imbalance between regulatory and effector arms of the immune system may initiate attacks in RRMS [2]. In PPMS, favoured hypotheses include a neurodegenerative process [3] or a neuroinflammatory process confined within the blood-brain barrier [4]. As outlined below, cumulative data from various investigators suggest an alternate, unifying concept, that premature thymic involution leads to a shift in peripheral T-cell homeostasis, which contributes to the pathogenesis of both RRMS and PPMS [5].

Homeostatic mechanisms maintain body systems in equilibrium in the face of change [6]. T-cell homeostasis balances thymic output of newly generated naïve T-cells, delivery of death and survival signals, differentiation of naïve T-cells into memory T-cells, and homeostatic proliferation. Homeostatic proliferation compensates for the progressive thymic involution and decreasing thymic output that occurs with age [7].

T-cell receptor excision circles (TRECs) are by-products of T-cell receptor gene rearrangement in the thymus and can be quantified as a surrogate measure of thymic output [8,9]. Several report reduced thymic output in adult-onset RRMS, based on findings of reduced T-cell TREC content [5]. Since TRECs are cytoplasmic DNA fragments that do not replicate during mitosis, both reduced thymic output and increased proliferation can reduce T-cell TREC content [8,9]. In a study of TRECs that excluded proliferation, we found that young patients with RRMS and PPMS have thymic export of naïve CD4 T-cells/day that is reduced to a level similar to controls 30-40 years older [10]. Balint et al. [11] expands on these observations, by showing that patients with pediatric-onset MS have reduced numbers of naïve and regulatory CD4 T-cells (Tregs) but increased numbers of memory CD4 T-cells; the naïve to memory CD4 T-cell ratios are similar to older controls. In comparisons with age-matched controls, Tregs from these patients had reduced suppressive capacity [11], which is also described in adult-onset MS [12,13]. The duration of MS was short in the pediatric-onset MS cohort but the shifts in both naïve CD4 T-cell and Treg numbers were similar to those in adult-onset MS. Since pediatric- and adult-onset MS is likely the same disease, one may conclude that premature thymic involution, not MS-associated chronic inflammation, causes the T-cell changes in both adult-onset and pediatric-onset MS [5,11].

The relevance of the T-cell changes to pathogenic processes in MS is of considerable interest. Two possibilities can be entertained and these are not mutually exclusive. Increased immune responses to both self and environmental antigens occur in pediatric-onset MS, and these responses are abnormally high even in very young patients [14]. Treg dysregulation could explain these non-specific T-cell responses [11], which may target the CNS in genetically susceptible individuals. Alternatively, premature thymic involution in MS may lead to increased homeostatic proliferation. Homeostatic proliferation induced by self-antigens inevitably expands autoreactive T-cells and thus has relevance to the initiation of autoimmune responses [15]. Recently, we calculated the potential contribution of proliferation to the naïve CD4 T-cell pools in healthy controls (n=68) and in patients with RRMS (n=68) and PPMS (n=20). We used a newly reported method based on TREC quantification, which demonstrated that ~ 90% of naïve CD4 T-cells in healthy adults is the product of peripheral T-cell proliferation [16]. In our study (manuscript in preparation), homeostatic proliferation generated on average ~ 92% of naïve CD4 T-cells in healthy controls, whereas the average magnitude of this proliferation was significantly greater in MS; ~ 95% in patients with RRMS and ~ 99% in patients with PPMS. These findings in MS are reminiscent of what occurs in an experimental mouse model in which lymphopenia induces increased homeostatic proliferation, which in turn initiates autoimmune diabetes [17].

What does premature thymic involution actually represent and when does it occur in MS? The normal human thymus grows only during the first year of life. Involution of thymic functional elements, including thymocytes and epithelial cells, then occurs in several phases that are independent of puberty. Phase 1 occurs from ~ age 1 to ~ age 10, during which the thymus involutes at a rate of ~ 5%/year. Subsequently, involution occurs at a rate of ~ 3%/year until middle age and then at less than 1%/year until old age [18-20]. The cohort reported by Balint et al. [11] had a mean age of MS onset of 13.5 years

(range 7-17 years). It seems likely that some process altered the thymuses of these patients either during phase 1 of normal thymic involution or shortly thereafter. In our comparisons of adult-onset MS with controls, daily thymic export of CD4 T-cells decreased exponentially with age in healthy controls, consistent with the effects of normal thymic involution; daily thymic export was about 2×10^8 CD4 T-cells per day at age 35 but had decreased to around 5×10^7 CD4 T-cells per day by age 60. In contrast, daily thymic export was not only low in the young patients with RRMS and PPMS (less than 10^6 CD4 T-cells/day at age 35) but thymic export remained at a constant and similar low level with increasing age [10]. In another study, RRMS patients had reduced but remarkable constant levels of CD4 T-cell TRECs with increasing age [21]. Together, these findings suggest that thymic function is independent of the normal phases of thymic involution in MS. The distribution of the thymic export data and the CD4 TREC data in MS suggest that functional changes in the thymus occur well before disease onset, probably in childhood or adolescence [10,21]. It is tempting to speculate in MS that some process in childhood/adolescence arrests normal thymic involution, alters Tregs, and reduces thymic functional volume so that thymic export is maintained at a low but constant level throughout life. Possibly, some unknown intrinsic alteration in the normal thymic developmental program induces this premature involution. Alternatively, some extrinsic factor may affect the thymus, e.g. Epstein-Barr virus (EBV), which is associated with pediatric-onset MS [22] and has the potential to bind to EBV receptors in the thymus [23]. If premature thymic involution occurs early in life and has relevance to the pathogenesis of both RRMS and PPMS, the question remains as to why MS begins in childhood in only a minority of patients.

References

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