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COMMENT

Dendritic cells as potential initiators of immune-mediated hypertensive disorders

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Current knowledge suggests the involvement of both innate and adaptive immunity in the pathophysiology of hypertension and hypertension-mediated organ damage (HMOD) [1]. Antigen-presenting cells (APCs), such as dendritic cells (DCs), play a pivotal role in the initiation of adaptive immunity, which may contribute to vascular and kidney injury in hypertension through T cell activation [2]. DCs are mainly derived from hematopoietic bone marrow progenitor cells and exist in an immature state in blood. After exposure to pathogens, DCs are activated to the mature form and migrate to lymph nodes with the capability to induce an adaptive immune response. Peripheral DCs are divided into two subsets, namely, myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). The former are characterized by CD11c expression and have a high capacity to produce proinflammatory cytokines (e.g., interleukin (IL)-6, IL-12 and IL-23), while the latter express CD123 and preferentially secrete type I interferon (IFN) to protect against viral infection. Both subsets of DCs play roles not only in infectious diseases but also in the development of autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus. However, the distribution of DC subsets may vary from disease to disease. An mDC/pDC imbalance was reported in coronary heart disease patients by Shi et al. in 2007 [3], but its significance has not been rigorously evaluated in the context of hypertension.

In the present study, Kubiszewska and colleagues compared the profile of DC between hypertensive and normotensive adolescents. Using flow cytometric analysis, they found that hypertensive subjects have a significantly higher percentage of mDCs and a lower percentage of pDCs than normotensive subjects [4]. The strength of their study is that they showed an association between various clinical data, including hemodynamic indices, and immune cell phenotypes. As data from younger patients are limited in this field, they provide important insights for our discussion of the mechanisms underlying the early development of hypertension. Previously, Hevia et al. demonstrated that genetic ablation of $CD11c^{high}$ APCs (i.e., mDCs) reduced blood pressure in mice treated with angiotensin (Ang) II plus high salt. Deletion of mDCs also prevented the decrease in IL-10 and FoxP3 mRNA expression in response to AngII plus salt treatment [5]. Therefore, the present result that CD11c-positive DCs are predominant in hypertensive children provides a clue for a therapeutic target to prevent HMOD. Since eliminating all dendritic cells would be harmful to the entire body, we need to find more selective therapeutic target molecules.

In the last decade, the role of A20, a zinc finger protein and ubiquitin-editing enzyme, has also been highlighted in the mechanism of DC-mediated autoimmunity. Kool et al. showed that A20-deficient mice with an inflammatory phenotype had increased conventional (myeloid) DCs, whereas the number of pDCs was decreased [6]. More recently, Lu and colleagues reported that specific deletion of A20 in CD11c-positive myeloid cells enhanced the accumulation of effector memory T cells in the kidney, which could promote blood pressure elevation [7]. In this study, the effect of A20 deletion was more marked in CD8-positive T cells than in CD4-positive T cells. In any case, A20 serves as an antigen presentation attenuator, and downregulation of A20 may serve as the underlying factor in DC-associated hypertension.

When considering the relation between innate immunity and hypertension, sodium intake is one of the most important factors [8]. Recently, Barbaro found that extracellular sodium enters DCs through amiloride-sensitive channels, leading to calcium overload in DCs. Activated DCs then produce superoxides, which induce the formation

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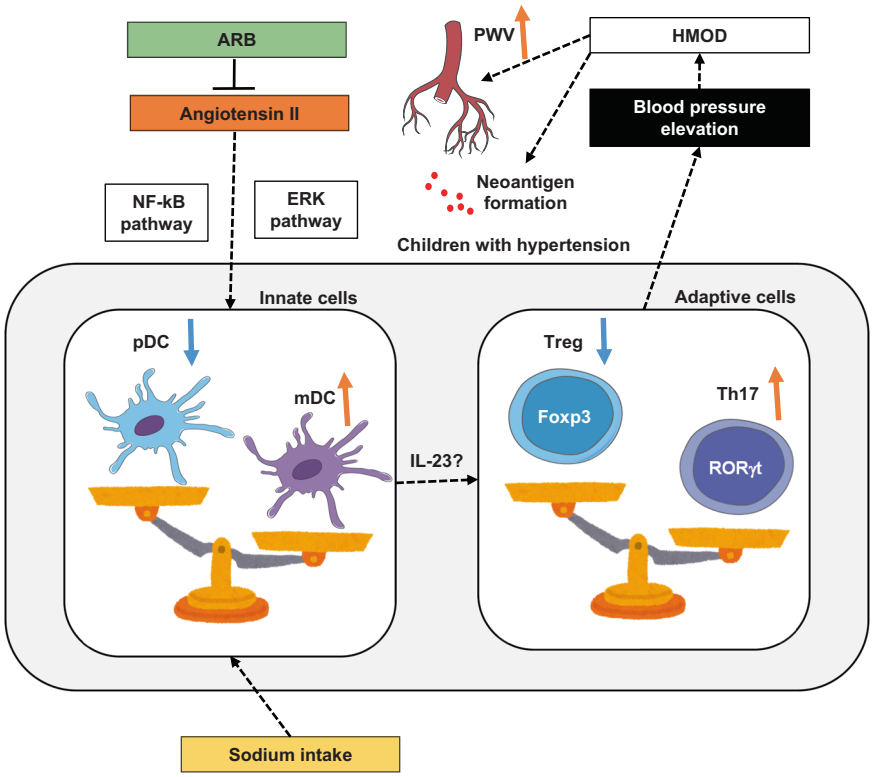

Fig. 1 Imbalance of dendritic cell subsets and its contribution to T cell-mediated hypertension. DC dendritic cell, pDC plasmocytoid DC, mDC myeloid DC, Treg regulatory T cell, Th17 interleukin-17-producing helper T cell, ARB angiotensin II type 1 receptor blocker, ERK extracellular signal-regulated kinase, NF-kB nuclear factor-kappa B, IL-23 interleukin-23, HMOD hypertension-mediated organ damage, PWV pulse wave velocity

of neoantigens (e.g., isolevuglandins) that are presented to T cells [9]. In the present study, the authors showed that the hypertensive population has a higher percentage of IL-17-producing helper T cells (Th17) than their normotensive counterparts. It is conceivable that hypertensive subjects are more likely to produce neoantigens by activated DCs, which in turn promote T cell immunity, leading to a vicious cycle of inflammatory response and HMOD. T cell activation can occur in either a TCR-dependent or cytokine-mediated manner.

Pulse wave velocity (PWV) is a marker of arterial stiffening and HMOD [10] and is correlated with the level of isoketal adducts in human aortic tissue [11]. The present study demonstrated that PWV was significantly higher in the hypertensive population and was positively correlated with increased expression of DC maturation/activation markers. Carotid artery intima-media thickness was also significantly higher in the primary hypertension group than in normotensive subjects. These results are in line with the recent report by del Mar Vila et al. showing that individuals with autoimmune disease have an increased risk of subclinical carotid atherosclerosis and stiffness [12]. In the present study, even the white-coat hypertension group showed significantly higher PWV than the normotensive group. In addition, certain DC characteristics in white-coat hypertension children resemble those of primary hypertension subjects, such as an increase in CD83-positive DCs and loss of CD86-positive pDCs. An interesting point here might be that the white-coat hypertension subjects had the highest body mass index compared to the other groups. The authors raised this issue as a main limitation of the present study. However, this finding seems to reflect the characteristics of young hypertensive patients in Poland and is rather suggestive in understanding the pathogenesis. Obesity is correlated with sympathetic nerve activity. It has been reported that sympathetic nerve hyperactivity precedes blood pressure elevation and usually exists in white-coat hypertension [13]. Therefore, DC induction may occur at an early stage of hypertensive disease and contribute to disease progression.

However, as stated in the Discussion, it is impossible to determine the causal relationship between altered distribution of DC and a hypertensive state from the presented results. Whether the skew in DC distribution can drive immune-mediated hypertension will only be clarified through interventional studies. As there is evidence that AngII directly and indirectly activates DCs via the ERK pathway [14] and NF kappa B pathway [15], the effect of AngII receptor blockers on the mDC/pDC ratio is of interest (Fig. 1). In addition, the relationship between gut microbiota and DC distribution in hypertensive patients is also an interesting research topic. Finally, since the sympathetic nervous system is associated with all aspects of hypertension etiology, including gut dysbiosis, future studies are expected to determine how renal denervation alters the circulating DC phenotype in human samples.

Compliance with ethical standard

Conflict of interest The authors declare no competing interests.

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