ABSTRACT

Type 1 diabetes (T1D) is an autoimmune disease with multifactorial aetiology that involves an attack of self-reactive cytotoxic CD8 lymphocytes on insulin-producing beta cells in the pancreas. In the T1D pathophysiology, both innate and adaptive immunity mechanisms cooperate in the development of inflammation leading to autoimmune destruction. Autoreactive T lymphocytes are the canonical destructors of the beta cells, and B cells produce autoantibodies; the innate immunity cells are considered the initiators of the pathological autoimmune reaction by promoting T and B cell activation.

Here, we provide evidence of both innate and adaptive immunity cell types dysregulation in patients with T1D, and that these changes occur before the onset of the disease. The changes in T regulatory lymphocytes (Tregs) and B cell subpopulations occur already in asymptomatic T1D first-degree relatives. During the first year after the onset of the disease, there is a gradual decrease in the neutrophil numbers in the periphery, which probably infiltrate the pancreas. We have focused more closely on the innate immunity dysregulation and its contribution to T1D pathogenesis. Initially, we describe that neutrophil products called neutrophil extracellular traps (NETs) are able to induce IFNγ-producing T cells through activation of dendritic cells (DCs). NET structures are predominantly composed of neutrophil DNA and antimicrobial proteins and are an important mechanism of antimicrobial defence; however, in recent years, NETs gained considerable attention in the field of autoimmune diseases as a source of potential autoantigens. Then, we show that T1D monocytes and DCs inappropriately react to the presence of DNA regardless of the origin, including microbial or endogenous sources, suggesting that aberrant recognition of DNA contained in NETs also participates in the inflammation associated with T1D. Our another study of DC biology in T1D patients focused on IL-27 signalling because the results of the RNA microarray assays revealed a profound increase in the IL-27 receptor subunit expression on myeloid DCs. The increased receptor expression was mirrored by an increase in STAT3 signalling and PD-L1 expression, suggesting compensatory mechanisms of ongoing inflammation in long-term treated T1D patients.

Overall, this doctoral thesis provides evidence of impaired aspects of immunity in T1D patients, including adaptive and innate immunity, and suggests that this orchestrated dysregulation occurs before the onset of the disease. Innate immunity dysregulation is also apparent in long-term treated T1D patients and is not associated with metabolic changes, suggesting that the changes are intrinsic and potentially determined genetically. Since presymptomatic patients benefit from early identification of the onset of the pathological processes leading to symptomatic T1D, we believe that information obtained in this work defines a solid background for future research.

Key words: type 1 diabetes; neutrophils, neutrophil extracellular traps; dendritic cells, DNA recognition, IL-27; T regulatory lymphocytes, B cells