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LETTER TO THE EDITOR

Comment on "Characterization of circulating leukocytes and correlation of leukocyte subsets with metabolic parameters 1 and 5 years after diabetes diagnosis"

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Dear Editor,

We read with interest the research article by Apostolopoulou et al. recently published in *Acta Diabetologica* [1], in which authors investigated the potential association between circulating lymphocyte subsets and different stages of type 1 diabetes (T1D) [1]. Authors reported that, among patients with T1D, $CD8^+$ cytotoxic T cells positively associated with a worse metabolic profile and the degree of inflammation, but not with insulin secretion in the 5 years following the diagnosis. The relationship between $CD8^+$ T cells and impaired metabolic and inflammatory profiles is likely to reflect an immune process accounting for lower C-peptide levels at the time of T1D diagnosis. As well, the percentage of $CD8^+$ T cells did not correlate with glucagon-stimulated C-peptide concentration at 5 years, thus confirming the progressive reduction of the secretory function of β cell due to the progressive islet destruction. Finally, after 5 years from diagnosis, neutrophil count from T1D patients associated positively with C-peptide and was lower than in T2D patients.

T1D is widely considered as an autoimmune disease, in which auto-reactive T cells progressively destroy β-cells among individuals with a major histocompatibility complex-restricted genetic susceptibility. On the other hand, a growing body of evidence is accumulating on a potential role for the innate immune system, too. In 2013, Valle et al. [2] conducted an elegant prospective study enrolling both pediatric and adult patients developing T1D. In their cohort, a mild peripheral neutropenia both preceded and accompanied the onset of T1D, irrespective of age; even more interestingly, the magnitude of neutropenia was associated in a positive fashion with the probability of developing diabetes [2]. Neutrophil impairment was manifest before the clinical diagnosis, thus probably reflecting the extent of the autoimmune process leading to frank diabetes. Anyway, in the 5 years following the clinical diagnosis, this process underwent a slow resolution along with the progressive destruction of the residual β-cell mass [2]. Potential mechanisms accounting for reduced circulating neutrophils in T1D are summarized in Table 1. This experimental evidence was tested in animal studies showing a close crosstalk between T cells and neutrophils, potentially via the formation of neutrophil extracellular traps (NETs) and the production of interferon-α by plasmacytoid dendritic cells, all these being likely limited in a narrow time window [3]. Moreover, evidence is emerging on the potential role of interleukin-17 and related cytokines secreted by T_H17 cells, which may induce granulopoiesis, thus promoting neutrophil proliferation and accumulation within the pancreas [4].

Starting from the very interesting article by Apostolopoulou et al. and taking into account the above-mentioned data, it appears clear that a reappraisal on the common vision of the pathogenesis of T1D is currently developing. The innate immunity plays an important role in modulating the clinical development of T1D; furthermore, its impairment detrimentally impacts on metabolism and inflammation even after T1D onset [1]. Indeed, a possible model of neutrophil infiltration may be driven by T_H17 cells and this means that the adaptive immune system could actively trigger the innate one. Besides, NETs are newly described pivotal mediators of neutrophil functions and cannot be forgiven when thinking

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Table 1 Potential mechanisms accounting for reduced circulating neutrophils in T1D

1	Defects in neutrophil output from bone marrow and differentiation due to hyperglycemia negatively impacting on bone marrow microenvironment
2	Augmented peripheral destruction due to increased neutrophil apoptosis or the production of anti-neutrophil antibodies
3	Tissue sequestration of neutrophils within small blood vessels of the exocrine pancreas or less frequently next to acinar cells in the exocrine tissue (this partially explaining the early, mild exocrine pancreatic insufficiency in T1D and the reduced volume of pancreas in autoantibody-positive individuals developing T1D)

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about the pathogenesis of T1D. Accordingly, Wang et al. reported, along with neutropenia, a marked increase in neutrophil granule products (i.e., neutrophil elastase and proteinase 3) at T1D onset, which was closely associated with NETosis and partly accounted for the reduction of neutrophil count [5]. Hence, although animal and human data appear still elusive to drive definite conclusions, they force us to consider neutrophils as equally important partners, particularly in the pre-clinical phase of T1D, as it is occurring for other autoimmune diseases, in which the close interplay of both innate and adaptive immune system can probably determine different disease phenotypes. We strongly believe that future studies aimed at investigating leukocyte subset modifications from the pre-clinical condition until the overt disease are warranted to deepen the knowledge of T1D pathophysiology. This effort is mandatory to bring quite old pathophysiological paradigms of T1D up to date and explore new alternative therapeutic strategies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Human and animal rights The authors declare that they have no competing interests.

Informed consent For this type of study formal consent is not required.

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