

Response to: 'Correspondence on 'Critical role of neutrophil extracellular traps (NETs) in patients with Behcet's disease' by Chen *et al*

We appreciate the interest of Chen *et al*¹ in our paper on the role of neutrophil extracellular traps (NETs) in patients with Behcet's disease (BD),² and read with great interest their work on the low-density granulocyte (LDG) as a potential source of NETs in BD.

LDGs, as opposed to normal density granulocytes, are characterized by their ability to be retained in the fraction of peripheral blood mononuclear cells after density gradient separation. LDGs were originally identified in patients with systemic lupus erythematosus³ and are now recognized in many diseases ranging from cancer to sepsis and autoimmunity.

First, in the paper of Chen *et al*, the authors report for the first time that patients with BD with an active disease displayed significant more LDG in the circulation than inactive patients and healthy donors. Interestingly, increased levels of LDG were also observed in patients with BD with vascular involvement compared with those without vascular involvement, suggesting LDG may contribute to vascular inflammation.

LDGs exhibit a proinflammatory phenotype, characterized by their capacity to secrete higher levels of interleukin (IL)-6, IL-8, tumour necrosis factor α and type I interferons⁴ and are, thus, of interest in BD pathophysiology. Moreover, they also induce increased endothelial damage and vascular dysfunction through their enhanced ability to synthesise and extrude NETs.⁵ NETs are chromatin fibers decorated with immunostimulatory nuclear and granule proteins and oxidized nucleic acids. NETs have been extensively investigated in autoinflammatory or autoimmune disease such as autoimmune vasculitis and in thrombotic events. In our paper,² we reported that patients with BD with active disease display more NETs. In particular, we showed that NET levels are increased in patients with BD with vascular involvement and contribute to the hypercoagulable state. In light of other diseases such as lupus, pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome⁵ or more recently in SARS-CoV-2 infection,⁶ it is tempting to speculate that in BD, LDG can contribute to the increased NET levels and that LDG-derived NETs are actively involved in the vascular inflammation. However, further experiments are needed to prove it.

Second, the authors provide further evidence that the LDG- to lymphocyte, as opposed to the neutrophil- to lymphocyte ratio (NLR), could be a better diagnostic tool to discriminate between patients with BD with or without vascular involvement and/or with or without active disease. NLR have been extensively studied in BD (as a prognostic marker, diagnostic tool, etc) with conflicted results. Thus, from a clinical point of view, LDG- to lymphocyte ratio could be of particular interest in determining the severity of BD and thus represent a more robust prognostic marker but further confirmation is needed. To our knowledge, the LDG-lymphocyte ratio has not been investigated in other diseases, autoinflammatory or not.

Overall, our paper² and the one by Chen *et al*¹ add further insight to the field of BD's pathophysiology and the role of LDG in innate immunity.

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Correction notice This article has been corrected since it published Online First. The provenance and peer review statement has been included.

Handling editor Josef S Smolen

Acknowledgements The authors thank David S Paul for editing this manuscript.

Contributors All authors wrote and reviewed the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

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To cite Le Joncour A, Saadoun D, Boulaftali Y. *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2020-219484

Received 16 December 2020

Accepted 17 December 2020



► <http://dx.doi.org/10.1136/annrheumdis-2020-219472>

Ann Rheum Dis 2020;**0**:1. doi:10.1136/annrheumdis-2020-219484

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