Göteborg, 2017

Human neutrophil heterogeneity: subsets, markers and autoantibodies

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen, våning 3, Guldhedsgatan 10A, Göteborg

Torsdagen den 19 januari 2017 klockan 9:00

av

Firoozeh Amirbeagi

Fakultetsopponent**: Professor Anders Bengtsson**
Institutionen för Kliniska Vetenskaper, Lunds Universitet, Lund

Avhandlingen baseras på följande delarbeten:

I. Welin A, Amirbeagi F, Christenson K, Björkman L, Björnsdottir H, Forsman H, Dahlgren C, Karlsson A, Bylund J. The human neutrophil subsets defined by the presence or absence of OLFM4 both transmigrate into tissue in vivo and give rise to distinct NETs in vitro. PLoS One. 2013 Jul 29;8 (7):e69575.

II. Amirbeagi F, Thulin P, Pullerits R, Pedersen B, Andersson BA, Dahlgren C, Welin A, Bylund J. Olfactomedin-4 autoantibodies give unusual c-ANCA staining patterns with reactivity to a subpopulation of neutrophils. J. Leukoc. Biol.2015 Jan 97(1):181-9.

III. Amirbeagi F, Thulin P, Björkman L, Andersson BA, Saalman R, Pullerits R, Welin A, Bylund J. CD177 (HNA-2a, NB1): Bimodal ANCA pattern of patient autoantibodies and investigations of involvement in neutrophil extravasation. *In Manuscript*.

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Human neutrophil heterogeneity: subsets, markers and autoantibodies

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Abstract

Neutrophils are phagocytic white blood cells that play essential roles in innate immunity and inflammation and that migrate to sites of infection to engulf and destroy microbes. Neutrophils have traditionally been viewed as a homogenous cell population, where all cells carry the same molecular cargo and have identical functions. Lately, this view is changing and distinct subsets of neutrophils are being recognized. The aim of this thesis was to characterize neutrophil subsets and investigate the role of their markers as anti-neutrophil cytoplasmic (ANCA) antigens.

The first paper investigated the recently discovered neutrophil subsets defined by the presence or absence of Olfactomedin-4 (OLFM4). We found that OLFM4 is indeed expressed by only a portion of the neutrophils from a given individual and that OLFM4 is a specific granule protein that can be exposed on neutrophil extracellular traps (NETs). We did not find any functional differences between the subsets *in vitro*, and the subsets migrated equally well into tissue *in vivo*, both to synovial fluid of arthritis patients and to aseptic experimental skin chamber on healthy skin.

During routine testing for the presence of ANCA in the circulation of patients with suspected autoimmune disorders, we found sera from two patients with diffuse inflammatory symptoms that displayed unusual staining patterns, reacting with only a subset of neutrophils. In the second paper we identified the target antigen as OLFM4, and this was the first report of autoantibodies towards this subset marker.

The third study began with two additional patient sera that gave rise to subset-restricted ANCA staining patterns. This time, we identified the target antigen as CD177, which is a known neutrophil subset marker and a known target of alloantibodies. CD177 has previously been shown to be of importance for transmigration of neutrophils *in vitro*. However, using synovial fluid from arthritis patients and the experimental skin blister model, we found no evidence for a major general role of CD177 in *in vivo* neutrophil transmigration.

In summary, we have characterized two *bona fide* neutrophil subsets and identified OLFM4 and CD177 as ANCA antigens.

Keywords: ANCA, OLFM4, CD177, Neutrophils

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