

Neutrophil recruitment in periodontal disease

Akademisk avhandling

som för avläggande av odontologie doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i Hörsal Arvid Carlsson, Academicum, Sahlgrenska akademien, Medicinaregatan 3, Göteborg, tisdagen den 26 oktober 2021, klockan 9.00.

av Agnes Dahlstrand Rudin

Fakultetsopponent:

Professor Iain Chapple

University of Birmingham, United Kingdom

Avhandlingen baseras på följande delarbeten

- I. Dahlstrand Rudin A, Khamzeh A, Venkatakrishnan V, Persson T, Gabl M, Savolainen O, Forsman H, Dahlgren C, Christenson K, Bylund J. *Porphyromonas gingivalis* produce neutrophil specific chemoattractants including short chain fatty acids. *Frontiers in Cellular and Infection Microbiology*. 2021 Jan 19. <https://doi.org/10.3389/fcimb.2020.620681>
- II. Dahlstrand Rudin A, Khamzeh A, Venkatakrishnan V, Basic A, Christenson K, Bylund J. Short chain fatty acids released by *Fusobacterium nucleatum* are neutrophil chemoattractants acting via free fatty acid receptor 2 (FFAR2). *Cellular Microbiology*. 2021 Aug;23(8): e13348. <https://doi.org/10.1111/cmi.13348>
- III. Dahlstrand Rudin A, Amirbeagi F, Davidsson L, Khamzeh A, Thorbert Mros S, Thulin P, Welin A, Björkman L, Christenson K, Bylund J. The neutrophil subset defined by CD177 expression is preferentially recruited to gingival crevicular fluid in periodontitis. *Journal of Leukocyte Biology*. 2021 Feb;109(2):349-362. <https://doi.org/10.1002/JLB.3A0520-081RR>
- IV. Dahlstrand Rudin A, Sanchez Klose FP, Komic H, Östberg A-K, Venkatakrishnan V, Christenson K, Bylund J. Proteomic characterization of neutrophil subsets distinguished by membrane expression of CD177. *In manuscript*

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Abstract

Neutrophils are the first immune cells to arrive in infected or injured tissues, where they engulf microbes and clean up cell debris. Periodontitis is one of the typical symptoms of both neutropenia and defect neutrophil functionality, suggesting an important role for these cells in maintenance of periodontal health. While representing a minor fraction of the leukocytes in the periodontal lesion, neutrophils are the dominating cell type in the periodontal pocket and gingival crevicular fluid (GCF). The overall aim of this thesis was to characterize factors modulating neutrophil recruitment from blood to GCF in periodontitis.

Neutrophil recruitment to the periodontal pocket is triggered by the bacterial species colonizing this site. Although previous studies have shown that subgingival bacteria trigger neutrophil chemotaxis, the bacterial chemoattractants responsible for this event remained to be identified. The aims of **paper I** and **II** were to identify soluble neutrophil chemoattractants released by the periodontitis associated bacterial species *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, and their corresponding neutrophil receptors. Chemotactic compounds present in culture supernatants of both bacterial species were identified as short chain fatty acids (SCFAs) specifically activating neutrophils via the short chain fatty acid receptor 2 (FFAR2).

CD177 is a neutrophil subtype marker with unknown function, expressed by 1–100% of circulating neutrophils depending on the donor. While CD177 has been proposed to facilitate neutrophil transmigration, this had not yet been demonstrated *in vivo*. The aim of **paper III** was to investigate whether CD177 expression affect neutrophil transmigration to GCF in periodontitis. The CD177⁺ subtype was enriched in GCF as compared to blood from the same donor, supporting an *in vivo* migration advantage of the CD177⁺ subtype to this site. Periodontitis patients also exhibited higher levels of CD177⁺ cells in blood as compared to healthy controls, which resulted in very high proportions of CD177⁺ cells in GCF. Considering this, functions differing between the subsets could influence destructive inflammation of the periodontal tissues. As CD177 may not be the sole factor contributing to functional differences between the subsets, further proteomic differences between CD177⁺ and CD177⁻ neutrophils were investigated in **paper IV**.

In conclusion, this thesis highlights SCFAs signaling via FFAR2 as factors involved in neutrophil chemotaxis triggered by periodontitis associated bacteria. Further, the CD177⁺ neutrophil subtype is preferentially recruited to GCF and functions specific for this subtype may be of importance for inducing (or suppressing) destructive inflammation in periodontal tissues.

Keywords: Neutrophil, periodontitis, *P. gingivalis*, *F. nucleatum*, SCFA, FFAR2, CD177, A1AT

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