University of Groningen

The kaleidoscope of microglia phenotypes

Kracht, Laura

DOI:
[10.33612/diss.194862555](https://doi.org/10.33612/diss.194862555)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Kracht, L. (2022). *The kaleidoscope of microglia phenotypes: Microglia transcriptional phenotypes from development to disease*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen. <https://doi.org/10.33612/diss.194862555>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

The kaleidoscope of microglia phenotypes

Microglia transcriptional phenotypes from development to disease

Laura Kracht

Research conduction Mainly at the Department of Biomedical Sciences of Cells & Systems, section Molecular Neurobiology, University Medical Center Groningen, University of Groningen, the Netherlands

Research subsidization Graduate School of Medical Sciences, Research School of Behavioural and Cognitive Neurosciences, Jan Kornelis de Cock-Hadders Foundation

Print subsidization University Medical Center Groningen, University of Groningen, Research School of Behavioural and Cognitive Neurosciences, the Netherlands

Printing Ridderprint BV, www.ridderprint.nl

Layout Laura Kracht

Cover design Vanessa Esquivel Salazar, www.behance.net/vanesquivel

Cover

The cover represents an illustration of a view through a kaleidoscope in form of the yin & yang symbol. Microglia are very dynamic cells, and their main aim is to maintain CNS homeostasis. When the CNS microenvironment gets in disbalance, microglia react with shifting from a homeostatic to an activated phenotype. These activated phenotypes are remarkably diverse and specifically tailored to the needs of the microenvironment at that given moment to restore CNS homeostasis. In that sense, the kaleidoscope is a metaphor for environmental-induced shifts of microglia phenotypes, whereby the diverse microglial phenotypes can be imagined as the manifold compositions of colorful crystals seen in a kaleidoscope, and a change in microenvironment (disbalance) is equivalent to a rotation of the kaleidoscope. The yin & yang symbol represent balance in a broad sense and in the here presented context, it reflects the endeavour of microglia to maintain CNS homeostasis. The colorful half of the yin & yang symbol is representing the microglial transcriptional phenotypes discovered over the last decade and in the presented dissertation, whereas the monochromic other half of the symbol is representing microglial phenotypes that we are not aware of yet.

This thesis was printed on FSC-certified recycled paper.

Copyright © 2021, Laura Kracht, The Netherlands. All rights reserved.

No part of this thesis may be reproduced or transmitted in any form or by any means, electronically or mechanically, including photocopying, recording or any information storage and retrieval system, without prior permission from the author and the publishers holding the copyright of the published articles.

university of
groningen

The kaleidoscope of microglia phenotypes

Microglia transcriptional phenotypes from development to disease

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of
the Rector Magnificus Prof. C. Wijmenga
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

10 January 2022 at 9.00 hours

by

Laura Kracht

born on 13 September 1990
in Göttingen, Germany

Supervisor

Prof. B.J.L. Eggen

Co-supervisor

Dr. S.M. Kooistra

Assessment committee

Prof. U.L.M. Eisel

Prof. P.J. Lucassen

Prof. S. Garel

Paranymphs

Dr. M. Borggrewe

N. Talma, MSc.

TABLE OF CONTENTS

CHAPTER 1: GENERAL INTRODUCTION.....	8
1. Microglia function and morphology	10
2. Microglia activation from a dichotomous to a multidimensional concept	12
3. Microglia origin in mice and humans	15
4. Microglia self-renewal and lifespan	17
5. Transcriptional phenotypes and functions of microglia during development	18
6. Microglia transcriptional phenotypes during adult homeostasis	24
7. Microglia transcriptional phenotypes during homeostatic disbalance	27
8. Epigenetics and immune memory	36
9. Outline of the thesis	39

CHAPTER 2.....	42
Human fetal microglia acquire homeostatic immune-sensing properties early in development

CHAPTER 3.....	70
Early-life stress impacts the adult microglia transcriptome under basal and inflammatory conditions

CHAPTER 4.....	98
Profiling microglia from Alzheimer's disease donors and non-demented elderly in acute human post-mortem cortical tissue

CHAPTER 5.....	130
Epigenetic regulation of innate immune memory in microglia

CHAPTER 6: GENERAL DISCUSSION AND FUTURE PERSPECTIVES.....	162
1. What are the functions of fetal microglia in utero?	164
2. Does reactivation of developmental microglia phenotypes take place in disease?	165
3. Does the development- and disease-associated subtype exist in humans?	167
4. The link between early life stress and later life	171
5. Future outlook on the era of single cell sequencing technology and microglia biology	174

APPENDICES.....	II
Glossary	IV
Graphical summary	VIII
English summary	X
Nederlandse Samenvatting	XIV
Deutsche Zusammenfassung	XVIII
Reference list	XXII
Curriculum Vitae	LXII
Acknowledgement	LXIV