Modulation of leukocyte homeostasis in atherosclerosis

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Stellingen behorende bij het proefschrift:

Modulation of Leukocyte Homeostasis in Atherosclerosis

1. Inflammatory processes responsible for the progression of atherosclerosis such as intravasation, extravasation and phenotypic differentiation of macrophages, are dynamic and can be modulated to induce lesion stabilization and disease resolution (this thesis).

2. The progression of atherosclerotic lesions from stability to vulnerability to rupture, is marked by a switch from wound healing into pro–inflammatory macrophage phenotypes (PLoS One. 2010 Jan;5(1):e8852).

3. Apoptotic cell death and survival exert both beneficial and detrimental effects on atherosclerosis, depending on intra- and extravascular leukocyte homeostasis, cell type and lesion stage (Arterioscler Thromb Vasc Biol, 2012, 32, 887-893 and this thesis).

4. Protection from apoptosis reduces inflammation in advanced atherosclerosis but causes early lesion expansion (Arterioscler Thromb Vasc Biol. 2012; 32: 887-893). Promoting macrophage survival in atherosclerosis would therefore be inappropriate to treat patients normally having lesions of all stages at any given time.

5. Challenging the current notion of macrophage death as cause of lesion vulnerability, manipulation of systemic leukocyte homeostasis and acute induction of macrophage apoptosis, cause macrophage turnover with concurrent atherosclerotic lesion stabilization in advanced atherosclerosis (this thesis).

6. Designing intervention therapies to prevent pro–atherogenic processes is complicated by the fact that most of these processes, including cell migration and apoptosis, are simultaneously crucial for resolution of inflammation and wound healing.

7. Single proteins contribute their molecular functions in pleiotropic and even antagonistic biological processes that build upon protein networks rather than on individual proteins.

8. Unlike lymphocytes, where phenotypic gene expression profiles are largely fixed by chromatin modifications and inherited by clonal expansion; macrophages can change their gene expression networks depending on the type, concentration, duration of exposure and priming by immunological stimuli (J Leukoc Biol. 2011 Apr;89(4):557-563).

9. The M1 vs M2 macrophage dichotomy, although useful for understanding, does not fully represent the biology of macrophages, which do not seem to conform to two fixed subsets, but rather activate molecular networks as diverse as their triggering factors.

10. More than 80% of potential new therapeutics tested in animals fail in clinical trials, causing hundreds of millions of dollars lost per year (Nature. 2014 March; 507:423-425). Investigators should be more aware of interspecies differences and several pitfalls regarding the use of animal models of disease that complicate their extrapolation in the context of human pathology.

11. 50% of human protein coding genes are each one linked to zero to fifteen scientific papers, comprising 8% of the publications indexed on NCBI. On the other side of the spectrum, with hundreds to thousands of publications each, the top 8% must studied genes are linked to 55% of indexed publications. The research community thus focuses most of its efforts on relatively few, known genes. Recognition of this phenomenon and a dramatic shift in the pattern of both scientific publishing and funding is required for a deeper understanding of the genetics of human disease.

12. Good understanding of the pertaining scientific field and its future trends should be requisite during the first year of a PhD, to make sure future doctorates direction their career and do not produce isolated fragments of science extemporaneous to their field but contemporaneous to its superseded predecessors.