Modulation of leukocyte homeostasis in atherosclerosis

Medina Rodriguez, I.A.

Abstract

The immune system is known for its vigorous response to foreign stimuli upon infection. But many of the recognition molecules and mechanisms involved in immune responses have no bias towards external stimuli, but also sense and respond to pathological and physiological changes of non infectious origin taking place within the body.

Responses of the immune system to homeostatic disturbances are determinant of the balance between disease progression or resolution; not only after bacterial or viral infection, but also upon the onset and development of pathological conditions including atherosclerosis; the leading cause of death in the world.

Aiming at defining potential immuno–therapeutic strategies to treat human atherosclerosis, the focus of this work was the modulation of immune processes determinant of atherosclerosis lesion progression or cessation in mice, such as hematopoiesis, diapedesis and intravasation, leukocyte differentiation, cholesterol uptake apoptosis and cell survival.

Modulation of these processes, by using bone marrow transplantation of hematopoietic stem cells with genetic deficiencies or over-expressing human or mouse engineered genes, demonstrated to alter the fate of atherosclerotic lesions at the balance between macrophage accumulation and lesion vulnerability versus resolution of inflammation and wound healing.

In particular, the experiments described in Chapter 2 indicate that hematopoietic deficiency of Hck and Fgr receptor tyrosine kinases, cause reduced diapedesis and skew immune responses towards inflammation leading to increased vulnerability of lesions to rupture despite reduced accumulation of macrophages. In contrast to these results, over–expression of iNAMPT, as described in Chapter 3, blocked the intravasation of monocytes, thereby reducing their availability to extravasate into atherosclerotic lesions, while simultaneously activating multiple pathways that promoted macrophage survival, resolution of inflammation and cholesterol efflux.

Regarding the balance between cell death and survival, induction of $CD169^{+}$ macrophage apoptosis caused transient extramedullar myelopoiesis, and atherosclerotic lesions that transitioned from lesion vulnerability to rupture to stabilization and wound healing (Chapter 4). Systemic and local induction of $CD115^{+}$ myelocyte apoptosis caused accumulation of apoptotic cells and macrophage turnover in atherosclerotic lesions. However, systemic induction of CD115+ myelocyte apoptosis led to features of lesion vulnerability, extramedullar myelopoiesis and altered circulatory and spleen leukocyte homeostasis not observed in the local application, as detailed in Chapter 5.

Overall, the results obtained shift the paradigm of macrophage accumulation as prime responsible factor of lesion vulnerability towards the notion of intra–lesion macrophage phenotype as crucial determinant of plaque stability.

This thesis demonstrates that processes responsible for the development and progression of atherosclerosis are dynamic and can be modulated to induce lesion stabilization and disease resolution. These results are promising for the development of novel therapeutics and challenge the current notion that atherosclerosis has a predetermined fate towards lesion vulnerability to rupture, which in humans results in thrombosis and clinical manifestations such myocardial infarction or stroke and sudden death.