ImmunoTools IT-Box-Cy55M-Award 2013

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The role of formyl-peptide receptors as pivotal checkpoints in atherosclerosis

The recruitment of leukocytes to the site of inflammation is dependent on a local gradient of chemotactic mediators. The formyl-peptide receptors (FPRs) are well known chemoattractant receptors initially identified to bind highly chemotactic *N*-formylated peptides. Those peptides originate from invading pathogens or from disrupted mitochondria during necrosis. Hence, FPRs play a role in both host defense against bacterial infection and in the clearance of damaged cells.

N-formylated peptides are not the only ligands that bind FPRs. Nowadays, numerous ligands are known to bind and induce cell activation via FPRs. Those G protein-coupled receptors interact with a large variety of structurally different ligands, including lipids, peptides and proteins, resulting in both pro- and anti-inflammatory signaling to possess important regulatory effects in multiple diseases. How FPRs may contribute to disease pathogeneses and host defense is currently not completely understood.

Our lab is focusing on atherosclerosis, a chronic inflammatory disease which induces the formation of lipid-rich lesions called plaques. Subsequently, plaque rupture can lead to life-threatening pathologies such as myocardial infarction and stroke. Because FPRs play a role in different stages of the inflammatory process we are interested in the role of those receptors in atherosclerosis.

There are three different human FPRs and two FPR orthologous are found in mice; FPR1 and FPR2. FPR1 and FPR2 are most abundant expressed on granulocytes. FPR1 is mainly indicated as a pro-inflammatory receptor. FPR2 has been shown to induce both pro- and anti-inflammatory signaling. Using ApoE-/- (leads to atherosclerosis in mice) and FPR-/- (FPR1-/- and FPR2-/-) mice we hope to reveal the role of FPRs in atherosclerosis. Whether we will find a pro- or anti-inflammatory role of the different FPRs in atherosclerosis we will try to establish mechanisms of FPR-signaling in atherosclerosis.

The ImmunoTools *IT-Box-Cy55M* would be of great benefit to us as it would be used to determine the cytokines that might play a role in FPR-signaling. For instance, IL-8 could play a role. *In vitro* experiments showed IL-8 upregulation via binding of serum amyloid A (SAA) to FPR2 (He et al. 2002) and elevated plasma levels of SAA accelerated disease progression in ApoE-mice (Dong et al. 2011). Furthermore, we will use those cytokines to interfere with

leukocyte homeostasis. Granulopoiesis (e.g. via G-CSF, TNF and IL-17), mobilization of leukocyte from the bone marrow (e.g. via CXCR2 ligands) and the clearance and homing of senescent leukocytes (e.g. via IL-12) may be important in FPR dependent disease progression/resolution since disturbance of leukocyte homeostasis has shown a clear correlation between the number of circulating neutrophils and the size of atherosclerotic lesions (Drechsler 2010).

He R, Sang, H, Ye R. (2002) Serum amyloid A induces IL-8 secretion through a G protein-coupled receptor, FPRL1/LXA4R. Blood 101: 1572-1581

Dong Z, Wu T, Qin W, An C, Wang Z, Zhang M, Zhang Y, Zhang C, An F. (2011) Serum amyloid A directly accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice. Mol Med. 17 (11-12): 1357-64

Drechsler M, Megens R, van Zandvoort M, Weber C, Soehnlein O. (2010) Hyperlipidemia-Triggered Neutrophilia Promotes Early Atherosclerosis. Circulation 122 (18): 1837-45