INSERM U1148 - Laboratory for Vascular Translational Science
Eicosanoids & Vascular Pharmacology
- CHU X. Bichat
46, Rue Henri Huchard 75018 Paris.
Thesis director: Dr Xavier Norel
Tel: 33 (0)1 40 25 75 29 – mail: xnorel@hotmail.com

Ph.D. Thesis Project:

Interactions between the myocardial tissue and coronary arteries in human: roles of specialized pro-resolving mediators and prostanoids

Inflammatory processes are involved in many cardiovascular diseases, such as myocardial infarction or acute coronary syndromes. These events influence the muscular reactivity (vascular and myocardial) as well as the remodeling process in heart and associated arteries. Bio-active lipids derived from Poly-Unsaturated Fatty Acids (PUFAs) include Omega-6 and Omega-3 Fatty Acids (FA) families. These molecules could be considered as time-dependent players of inflammation reaction, where Omega 6 will induce inflammation while in a Omega 3 will be later responsible for its resolution.

Among Omega-6 FA members, which are considered mostly as mediators of inflammation, we find prostanoids (regrouping Prostaglandins (PG) and Thromboxane (Tx)). These molecules are derived from Arachidonic Acid which is the substrate of Cyclooxygenases (COX-1; COX-2) (Ozen et al, 2017; Ricciotti et Fitzgerald, 2011).
Omega-3 fatty acid (such as DPA, DHA, and EPA[1]) but also some Omega-6 FA (HETE[2], lipoxins) have been characterized to have a cardioprotective effect. Indeed, these molecules are the precursors of the Specialized Pro-Resolving Mediators (SPMs, e.g. Resolvin, Protectin, Maresin et Lipoxin), involved in the resolution of the inflammation (Serhan, 2014).

Aim of the study:

Our study will focus on investigating the functions of PGs and SPMs and their interactions between the myocardial tissue and the adjacent coronary arteries in the inflammatory process linked to the cardiovascular diseases.

PGE2, PGD2, PGI2, and TxA2 have a major role in the inflammatory response in cardiovascular disease (Gomez et al, 2013; Norel, 2007). However, their physiological influence has not yet been studied in human vessels, such as coronary arteries, using ex-vivo experiments (Ozen et Norel, 2017). Our preliminary results show that PGE2, via its EP3 receptor, induces contraction in isolated human coronary arteries (Ozen et al, 2015). In human vessels, PGE2 produced under inflammatory conditions, stimulates proliferation of smooth muscle and MMP[3] expressions (Gomez et al, 2016; 2013; Norel et al., 2017).
Concerning the cardiac tissue, some pieces of evidence in Human and Murine models suggest that PGE2 stimulates (via its EP2/EP4 receptors) the proliferation of cardiomyocytes, inducing cardiac hypertrophy (Chien et al, 2014; Schaub et Hefti, 2007). An opposite effect has been described in murine models for the EP3 receptor, suggesting a cardioprotective role of PGE2, by reducing the infarct size without causing hemodynamic effects (Thiemermann et Zacharowski, 2000; Zacharowski et al, 1999). The same effect has been shown with 15d-PGJ2 (a metabolite of PGD2) which can activate PPAR-alpha/gamma receptors and reduce myocardial lesion in myocardial ischemia-reperfusion model (Wayman et al, 2002).

[1] DPA: Docosapentaenoique Acid – DHA: Docosahexanoic Acid - EPA: Eicosapentaenoic Acid
[2] HETE: Hydroxyeicosatetraenoic Acid
[3] MMP: Matrix metalloproteinases

On the other hand, regimen rich in Omega-3 FA have shown to partly suppress inflammatory events known to produce vascular endothelial damage leading to atherosclerosis and thrombosis (Poorani et al. 2016). In the same way, studies on different human tissues show that Omega-3 FA inhibit migration and subsequent proliferation of smooth muscle cells, fibroblasts and macrophages, preventing atherosclerosis and fibrosis. (Das, 2009). Thus, in a murine model, some evidence shows that EPA/DPA treatments can suppress the proliferation of vascular smooth muscle cells of rat aorta (Terano et al, 1996).
Furthermore, it has been shown that some SPM such as Resolvin E1 and D1 could prevent the development of fibrosis in an obstructed kidney mouse model (Qu et al, 2012), and that Resolvin D1 can also improve the ventricular function after myocardial infection in mice (Kain et al 2015).

These interesting results should be verified on human models, especially on coronary arteries and cardiac tissues, taking into account the inflammatory state. The research perspectives could be enlarged with metabolomic and proteomic analysis of treated preparations with Omega-3/6 FA-derived products, giving us the opportunity to discover related signaling pathways.
Moreover, the interaction between prostanoid pathway and the production of SPMs could be of interest to be investigated in our models, since small doses of Aspirin can induce the production of specific "Aspirin-Triggered" SPMs after acetylating the COX-enzyme (Poorani et al. 2016).

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Wayman et al, 2002; PMID: 12118185
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Das, 2009; PMID: UNK
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Qu et al, 2012; PMID: 22610993
Kain et al 2015, PMID: 25870158