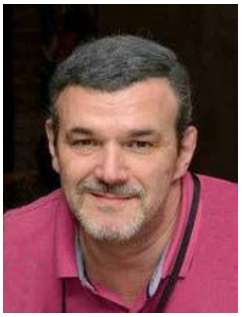
Lipid Signaling in Innate Immunity and Inflammation

Bioactive Lipids and Lipidomics



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Monocytes and macrophages are cells of innate and adaptive immunity that participate and govern inflammation by producing a number of mediators, including cytokines, chemokines, and bioactive lipids such as arachidonic acid and its oxygenated derivatives, collectively known as the eicosanoids. Work in our laboratory aims at delineating the mechanisms through which these bioactive lipids mediate inflammation and contribute to disease pathogenesis. The eicosanoids derive from the enzymatic oxygenation of free arachidonic acid, a compound that, initially present in esterified from in membrane phospholipids, is released in activated cells by several pathways. The phospholipase A_2 pathway constitutes the most important one.

Cardiovascular disease is one of the most frequent inflammatory diseases. Atherosclerosis is the primary cause for cardiovascular disease, and diabetes increases the risk several-fold by enhancing the formation and/or progression of atherosclerotic lesions, a process in which abnormally-activated monocytes and macrophages appear to play a major role. In diabetes, these cells appear to be in a proinflammatory state, releasing elevated amounts of cytokines and eicosanoids which perpetuate the inflammatory condition. Monocytes/macrophages from diabetic patients have been found to exhibit enhanced expression of Toll-like receptors TLR2 and TLR4. These receptors sense bacterial pathogens but also endogenous danger molecules such as saturated free fatty acids, typically present at elevated amounts in obese individuals.

The first step in the initiation of an atherosclerotic plaque is the activation of the endothelial cells that line the inside of the vessel wall. This activation may obey to different causes and one of them is, precisely, elevated sugar in blood, i.e. diabetes. Endothelial cells then release a variety of products that attract circulating monocytes. These cells attach to the endothelium and migrate through it towards the tunica media, composed of smooth muscle cells. Once within the vessel wall, monocytes differentiate into macrophages, which synthesize and secrete an enormous amount of inflammatory mediators that perpetuate damage. In addition, the macrophages become foam cells by ingesting lipids, particularly cholesterol, and storing them into cytoplasmic lipid droplets. As time passes, smooth muscle cells start to

proliferate and move into the macrophage-rich plaque. The plaque may eventually rupture, leading to the formation of thrombi or emboli that cause heart attack or stroke.

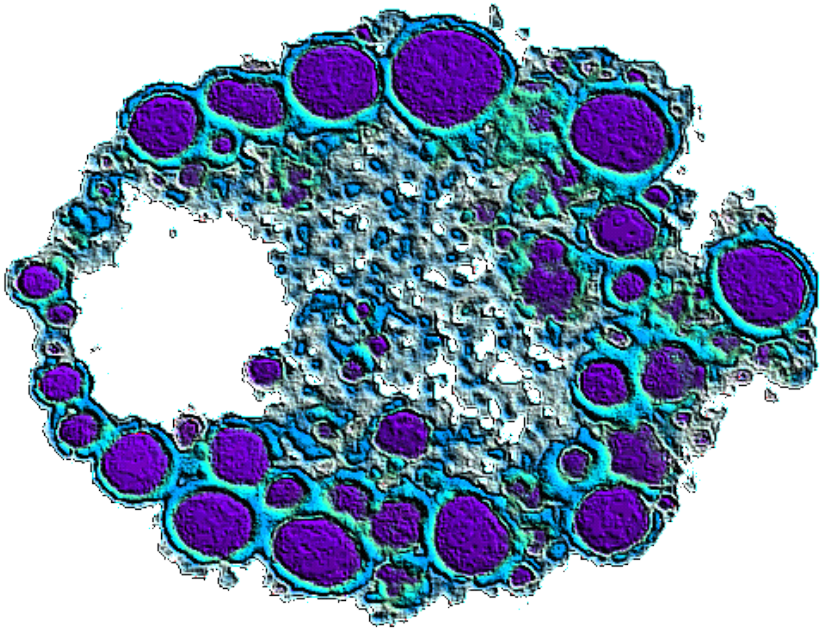

Figure 1 – Fat-laden human macrophage

Within this general framework, there are currently four major lines of research in our laboratory, which are briefly described as follows:

- The first line focuses on the cellular regulation of phospholipase A_2 and the biochemical mechanisms involved in the biosynthesis of eicosanoids by activated monocytes/macrophages. There are multiple phospholipase A_2s in cells and our goal is to delineate the role of each of these forms in eicosanoid production by cells responding to TLR agonists (1-5).

- A second line focuses on the biosynthesis and degradation of lipid droplets during cellular activation. Lipid droplets are the cytoplasmic organelles where monocytes/macrophages store fat (see Figure 1), yet they also serve many other interesting roles, e.g. they may function as docking platforms for a number of enzymes involved in lipid signaling or as an intracellular site for the synthesis of lipid mediators (6,7).

- The third line focuses on the application of mass spectrometry-based lipidomic strategies for the identification and quantification of cellular lipidomes. In this regard a major goal of our research is to determine the origin and identity of the individual phospholipid molecular species that are produced under different conditions, as a key step to address their biological roles in cells (8-14).

- A final line of research, which is relatively new in our lab, concerns on the role of omega-3 fatty acid derivatives as deactivators of monocyte/macrophage activation via their antagonistic effects on inflammasome activation or other mechanisms.

All lines of research rely heavily on biochemical and analytical methods to identify specific reactions and the mechanisms through which the products of said reactions are formed. With this information, we expect to delineate pathways responsible for disease. In summary, in our laboratory we combine a range of chemical, biochemical, pharmacological, and molecular cell biology techniques to study pathophysiologically-relevant problems involving alterations in lipid metabolism and signaling.

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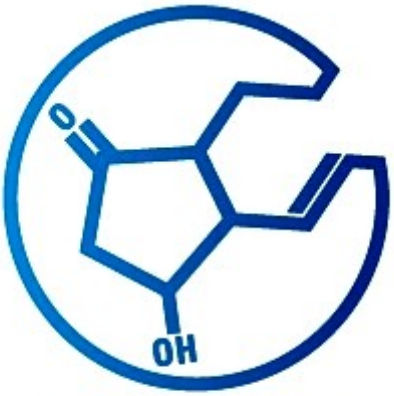

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