Lipid Metabolism and Inflammation Subline.
Research Support History*

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Phagocytic cells produce substances with high oxidant capacity during inactivation and phagocytosis of invading pathogens. However, an uncontrolled production of these oxidants may lead to damage and hence, may constitute a very serious problem for the host. Oxidative damage usually occurs in parallel with the mobilization of free fatty acids such as arachidonic acid (AA) from membrane phospholipids. It is likely that these two processes are causally related, although the mechanisms involved are not understood. The current research proposal focuses on the elucidation of the molecular mechanisms through which phospholipase A\(_2\) activity is augmented during oxidative stress and the apoptotic processes that ordinarily ensue. Previous studies by the principal investigator have shown that calcium-independent phospholipase A\(_2\) (iPLA\(_2\)) is responsible for the mobilization of free fatty acids during oxidative stress. Based on these previous findings, we propose to study: (i) the molecular nature of the oxidized phospholipid species that are produced during cellular exposure to hydrogen peroxide, and their potential effects on iPLA\(_2\); (ii) molecular mechanisms associated to hydrogen peroxide-induced apoptosis; (iii) changes in iPLA\(_2\) activity and/or physical state that may account for its enhanced capacity to destroy membrane phospholipid; (iv) role of iPLA\(_2\)-derived products, free fatty acids and lysophospholipids, during oxidant-induced apoptosis; and (v) role of iPLA\(_2\) on the phagocytosis of apoptotic cells by phagocytes. Publications derived from this grant (1-10).

(2) Linking Inflammation to Obesity: Regulatory Roles of Magnesium-dependent Phosphatidic Acid Phosphatase in Macrophage Physiology (Spanish Ministry of Science and Technology, ref. SAF2007-60055) (2007-2010)

When an inflammatory focus is established, various cell types migrate to the inflamed site to begin reactions of healing and repair. Macrophages are among these cells and play prominent roles in the initiation and resolution of the inflammatory process. Although much effort has been put into understanding the basic molecular mechanisms underlying macrophage activation during innate immune reactions, there are still key aspects that remain to be elucidated, in particular many affecting the lipid metabolism. This research proposal focuses on the study of the role of phosphatidic acid phosphatase (PAP) during macrophage activation and survival. The sequence of PAP, a key enzyme in the biosynthesis of glycerophospholipids and triacylglycerol, has recently
been elucidated and, interestingly, found to be identical to the protein known as lipin, a protein known to regulate obesity. Overexpression of lipin in mice leads to obesity and deletion of the gene shows marked changes in adipose tissue distribution. It is well known that obesity is a leading factor for the induction of chronic activation of the innate immune system and that macrophages may be the relevant cell type involved by virtue of its capacity to release a wide array of proinflammatory cytokines under obesity conditions. Chronic macrophage activation under these conditions is thought to ultimately lead to insulin resistance, glucose intolerance and even diabetes. Studies on of PAP/lipin may help uncover novel routes of interaction between obesity and inflammation. Accordingly, we propose to study (i) the expression of PAP/lipin in human macrophages; (ii) the subcellular localization of the enzyme; (iii) activity regulation by phosphorylation; (iv) effects of PAP/lipin overexpression and silencing on general macrophage physiology, and (v) the innate immune response of mice lacking PAP/lipin and diet-induced obese mice. These studies will aid to better understand macrophage biology and to strengthen the link between obesity and inflammation. In addition, it is expected that these studies help uncover novel molecular targets with therapeutic potential for the treatment of inflammation. Publications derived from this grant (10-23).

(3) Regulation of Inflammation by Lipin, an Enzyme Involved in Obesity (Regional Government of Castile and Leon, Health Department, ref. BIO39/VA04/10) (2010-2011)

During inflammation, different cellular types move to the inflammatory foci to help in the tasks of repairing and cleaning. Monocytes/macrophages are one of these. Although the scientific community has dedicated much effort to the study of these immune cells, a major part of the molecular mechanisms that govern their activation/deactivation actions during inflammation remain unanswered. The present project focuses on the role of a key enzyme in lipid metabolism, the phosphatidic acid phosphatase (PAP), in activation and survival of the macrophages. PAP has recently been sequenced and identified to be the same as lipin, an enzyme whose overexpression produces obesity, and its absence produces loss of adipose tissue. Obesity is now known to induce a chronic activation of the innate immune system, and the macrophages are the cells chiefly implied in the production of proinflammatory cytokines under these settings. Study on the biological role of PAP/Lipin could unveil new connections between obesity and inflammation. Publications derived from this grant (24).

(4) Role of Lipin in Animal Models of Obesity and Infection (Regional Government of Castile & Leon, Education Department, ref. CSI168A12-1) (2012-2013)

In recent years, obese and overweight (20%) population is increasing at an alarming rate in the Community of Castilla and León, which currently ranks 5th in childhood obesity in Spain. In addition to being an important cardiovascular risk factor, obesity is also associated with diabetes and other diseases that decrease the quality and life expectancy. Obesity is associated with low grade inflammation where macrophages play an important role by producing pro-inflammatory cytokines. It is thought that this activation leads to insulin resistance, diabetes and glucose intolerance. Although the scientific community has devoted much effort to the study of these cells of the innate immune system, there is still not much known on the molecular mechanisms that govern its activation/deactivation during the inflammatory response. This project focuses on the study of the role of an important enzyme of lipid metabolism, phosphatidic acid phosphatase, also known as lipin, in the activation of macrophages and its role in inflammatory models and obesity-metabolic and immune. Our specific objectives are: 1) to establish the role of lipin in macrophage activation induced by fatty acids in adipose tissue in models of obesity; 2) to study its role in animal models of inflammation induced by bacteria or its derivatives and, 3) to dissect the signaling pathways involving lipina. This research will provide us with to better understanding of macrophage activation and unveil new strategies for the treatment of the aforementioned diseases.
Macrophages are key cells that help in the management of inflammation, but they can also contribute to exacerbating it by generating excessive pro-inflammatory molecules. The study of the signaling programs that operate during macrophage activation could give us a clue to manipulate it, and could help us generate new drugs and treatments for the cure and prevention of chronic inflammatory diseases. The overall goal of this project is to define the role of lipin, a phosphatidate phosphatase, in the regulation of macrophage biology. Lipin can act as a signaling molecule and as a fat-storage mediator. We propose to study the mechanism by which lipin changes the activation state of macrophages and its impact in animal models of inflammation. The specific aims are: 1) to define which and how the metabolites that are generated and cleared by lipin after macrophage stimulation influence the generation of pro-inflammatory molecules and their repercussion on pulmonary and peritoneal inflammation models, 2) to define the role of lipin during macrophage activation by fatty acids and their impact in high fat diet-induced inflammation, 3) to define the protein domains and mechanisms by which lipin attaches and/or translocates to subcellular compartments, and 4) to define the role of lipin in the formation and maintenance of lipid droplets. Completion of this proposal may open new avenues for the control of excessive macrophage activation and hence, for the future management of inflammatory-related illnesses. Publications derived from this grant (24-30).

REFERENCES


