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Trash talk by fat: Chemerin as a ROS provocateur in the Vasculature

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Adipose tissue is increasingly being considered as more than just a storage depot for sources of metabolic energy. We are learning that adipose tissue is dynamic, capable of remodeling, of shifting its metabolic program when challenged and of contributing to both health and disease. Of keen interest is the secretome of adipose depots. With the discovery of Leptin in 1994, a new avenue of research into adipokines and the cardiovascular system was born. A rich group of adipocyte-derived proteins is being discovered as important to cardiovascular function. In the paper by Neves and colleagues in this issue (1), chemerin is the protein of focus.

Chemerin was discovered less than twenty years ago in skin, not in adipocytes (2). Tazarotene-induced gene 2 (TIG2 or chemerin) was initially described as being upregulated by retinoids in skin. The ability of chemerin to function as an adipokine and regulate adipogenesis through a receptor (IUPHAR recognized as ChemR23 in 2013) was supported ten years later in 2007 by several groups (3,4,5). The significant positive association, observed by multiple groups, of circulating chemerin levels with obesity makes chemerin a compelling target to investigate relative to the pathologies of obesity (6). To be sure, a focus on chemerin in experimental science has been in population studies which provide the foundation for wanting to understand the biology of chemerin.

Two recent studies support the biology of chemerin extending to the vasculature, and set the stage for the current manuscript that is the focus of this commentary. Chemerin incubation with isolated, cleaned (no perivascular adipose tissue) rings of normal rat thoracic aorta *in vitro* increased the sensitivity of the aorta to endothelin -1 (ET-1) but not to the adrenergic agonist phenylephrine (7). Removal of the endothelium enhanced the procontractile action of chemerin, an action that utilized signaling through the extracellular signal regulated kinase or Erk Mitogen activated protein kinases (MAPK). Studies from our lab support chemerin in promoting contraction, but in a slightly different way. We discovered chemerin expression in perivascular adipose tissue (PVAT) (8). Chemerin-9 was used as a biologically active agonist at ChemR23, and found it caused concentration-dependent contraction from baseline in the endothelium-denuded rat arteries (aorta and superior mesenteric artery). This same paper presented the original description of CCX832, a small molecule antagonist against ChemR23 developed by ChemoCentryx. Expression of ChemR23 has been observed

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None

in both smooth muscle cells and endothelial cells (9,10), and thus the balance of the actions of chemerin in these two neighboring cells types is of interest. The present manuscript investigates these two very cell types, and uses CCX832 to implicate ChemR23 in actions stimulated by chemerin. The endpoints investigated in this present report are different biological actions of chemerin in the vasculature than previously addressed, namely growth, apoptosis and inflammation.

Cultures of human microvascular endothelial cells and human vascular smooth muscle cells were the model of the present study. Exogenous, commercially available chemerin increased levels of superoxide in a Nox-dependent manner in endothelial cells, thereby implicating an enzyme that has enormous interest in terms of vascular inflammation and remodeling. This was associated with activation of inflammogen production, monocyte attachment as well as activation of the Erk MAPK pathway. A key experiment is the blockade of chemerin's action with the ChemR23 antagonist CCX832, and these data support ChemR23 transmitting an inflammatory signal. On the 'flip-side' of endothelial function, chemerin caused phosphorylation of the active/inhibitory sites of eNOS which reduced overall eNOS activity. This effect was modest, but would tip the balance of chemerin's action in being pro-inflammatory in the endothelial cell under these conditions. A later paper by the same group supported chemerin's ability to reduce biologically active NO production through monomerizing eNOS, reducing mRNA for GTP cyclohydrolase I (rate limiting enzyme for the eNOS cofactor BH4) and reducing the ability of guanylate cyclase to signal in an NO-dependent manner (10).

As in the endothelial cell culture tested in the present study, chemerin stimulated production of ROS in the human vascular smooth muscle cells, also in a Nox- and ChemR23-dependent manner. Markers of proliferation were elevated by chemerin, as was caspase-3 and DNA fragmentation, both outcomes of apoptosis. Pharmacological inhibitors used in these assays support the role of Nox, the MAPK and phosphoinositide-3-kinase pathway in these events.

These studies strengthen the biological argument for chemerin as an endogenous inflammogen by demonstrating that human and obese/diabetic mouse adipocyte-derived medium also elevated ROS generation in the vascular smooth muscle cells in a ChemR23-dependent manner. A caution in these experiments is that the human adipocytes were stimulated with aldosterone; no data were shared from adipocytes not stimulated with aldosterone.

The jury is still out on this provocateur

The literature on chemerin has largely been devoted to studies supporting the inflammatory nature of chemerin. The present study certainly provides sound evidence of this possibility. However, chemerin and chemerin agonists also possess anti-inflammatory functions. Highlighted in a study by Cash et al (2008) not long after chemerin's discovery in adipose tissue, chemerin and a chemerin derived peptide (chemerin-15) were shown to protect mice from the inflammation stimulated by a zymosan challenge, and did so in a manner dependent on activation of ChemR23 (11). Similarly, resolvin E1 has been proposed to exert at least part of its anti-inflammatory effects through activation of ChemR23 (12). These findings raise the fascinating possibilities of lipids and proteins both interacting with

ChemR23 in a potentially physiological (or pharmacological?) antagonistic fashion. Of interest is knowledge of whether chemerin and resolvins would compete for the same site of ChemR23 in the endothelial cell and vascular smooth muscle cell (orthosteric or allosteric interaction?). This interaction, as well as the relative availability of both chemerin and resolvin E1, would dictate the ultimate outcome for whether activation of ChemR23 in each cell type is overall inflammatory or anti-inflammatory.

Looking to the future

Essential to understand the role played by chemerin in cardiovascular function and disease will be identification of those peptides made by adipose depots. Given that multiple isoforms of chemerin can be biologically produced (6), are they the same complement of peptides in each depot, or do different depots contribute differently? Are both inflammatory and anti-inflammatory isoforms of chemerin made? What regulates the production of these peptides, and tips the scale to pro- or anti-inflammatory actions? How does resolvin E1 (or does it?) play a role in tempering the actions of chemerin? Which depot (visceral? perivascular adipose tissue?) should the cardiovascular researcher be most concerned with? Additionally, the liver is a source of chemerin and understanding its potential 'connection' to the inflammatory actions in the cardiovascular system would make for fascinating research. In this same vein, the coordination of action of the three different receptors for chemerin that have been recognized needs to be better understood: ChemR23, G protein-coupled receptor 1 and chemokine (CC motif) receptor-like 2. It is significant to understand that chemerin is just over 20 years old, and has already raised a host of important questions that our community can answer.

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Figure 1. Depiction of potential sources (liver, adipocyte) of chemerin, which can interact with the heptahelical receptor ChemR23 in both the endothelial and smooth muscle cell. EC = endothelial cell, SMC = smooth muscle cell.