Resolution pathways in inflammation: the devil in the adipose tissues and in the details. Focus on “Diversity of lipid mediators in human adipose tissue depots”

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Inflammation is an essential and protective response to infection and tissue injury. Neutralization of the offending insult activates endogenous pathways, which dampen the acute inflammatory response and trigger repair of the affected tissues to regain homeostasis. However, these do not occur in many patients. Indeed, excessive or dysregulated inflammation together with impaired repair contribute to persisting tissue damage that underlies many pathological conditions, including vascular and renal diseases and diabetes (10).

Over the past 10 years, we have come to realize that similar to mounting an inflammatory response, resolution of acute inflammation is also an active process that involves a complex series of tightly controlled events (11, 12). A central paradigm has been that efficient resolution of inflammation depends on inhibition of leukocyte influx into the inflamed site, promotion of apoptosis in emigrated inflammatory cells and their rapid clearance by macrophages and regeneration of disrupted tissue structure. Groundbreaking work has characterized lipid and protein/peptide mediators that orchestrate these events and assure return to normal physiology. A series of elegant studies using self-resolving inflammatory exudates and lipidomics led to identification of a novel genus of lipid mediators derived from the metabolism of long-chain polyunsaturated fatty acids as important “specialized proresolving mediators” (SPM) (11, 12). Among SPM are lipoxins derived from the omega-6 fatty acid arachidonic acid, and resolins, protectins and maresins derived from the omega-3 fatty acids eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, which have been reported to facilitate resolution of acute inflammation in a variety of experimental models and clinical settings (11, 12). Accumulating evidence indicates the ability of SPM to counter, among others, the potent proinflammatory actions of eicosanoids derived from arachidonic acid through the cyclooxygenase and lipoxygenase pathways, including prostaglandins and leukotrienes. It is plausible that the balance between pro- and anti-inflammatory/proresolving lipid and peptide mediators would determine the outcome of acute inflammation. There is evidence that the proinflammatory prostaglandin (PG) E2 and PGD2 stimulate formation of lipoxin A4 (LXA4) during acute inflammatory exudate formation, thereby activating resolution mechanisms (9).

In addition to being the largest source of fuel in the body, adipose tissue functions as an endocrine organ to regulate whole body energy metabolism and insulin sensitivity (6). Adipocytes together with resident macrophages are also a source of inflammatory cytokines that contribute to chronic low-grade inflammation that is linked to development of diabetes and its sequela, including peripheral vascular disease. Recent studies detected decreased SPM biosynthesis in adipose tissues from obese-diabetic mice (4). Conversely, treatment of these mice with LXA4, resolvin D1 (RvD1), or RvD2 has been shown to improve insulin sensitivity (1, 8). Data emerging from in vitro and animal studies will, however, need to be validated in the clinical setting.

In this issue of American Journal of Physiology-Cell Physiology, Claria and colleagues (3) fill an important gap in our knowledge by demonstrating regional diversity in lipid mediator profiles in perivascular and subcutaneous fat of patients that underwent lower extremity amputation due to (presumably diabetes-associated) peripheral vascular disease (PVD) compared with lipid profiles in peri-wound and nonwound subcutaneous fat collected from patients without clinical evidence for PVD who were undergoing elective hip or knee replacement. Using liquid chromatography/tandem mass spectrometry-based metabolo-lipidomics, the authors detected reduced levels of protectin D1 (PD1) and its intermediate precursor, which exert protective actions in vascular inflammation, in subcutaneous adipose tissue from patients with PVD. These changes occurred in parallel with increased inflammatory adipokine levels, implying an imbalance in the formation of pro- and anti-inflammatory mediators. Although RvD1, RvE1, and PD1 were reported to directly regulate adiponectin secretion from murine adipose tissues (4, 8), the authors did not detect any inverse correlations between adipokine and individual SPM levels, indicating a more complex link between these mediators. Intriguingly, perivascular adipose tissue from PVD patients exhibited higher SPM levels than subcutaneous fat, whereas formation of proinflammatory prostanooids apart from leukotriene B4 (LTB4) was similar in perivascular and subcutaneous adipose tissue. These findings are consistent with a shifting of the balance towards resolution in this location. However, whether these changes are specific for PVD and their pathophysiological significance in the pathogenesis of PVD remain to be investigated.

Another interesting finding of this study is that peri-wound subcutaneous adipose tissue showed markedly enhanced production of SPM, as well as the proinflammatory eicosanoids LTB4, PGE2, and PGD2. Since the lipid analyses were performed only at one time point, it is uncertain whether increased SPM production represents a counterregulatory mechanism of the inflammatory response to tissue injury at this time point. Since LTB4 binds to the same receptor BLT1 as RvE1 and RvE2 (12), high local levels of LTB4 may temporarily override the proresolving actions of SPM. This possibility is supported by data from studies on the formyl-peptide receptor FPR2/ALX in human neutrophils, where LXA4 was reported to override the proinflammatory actions of serum amyloid A and vice versa depending on their relative concentrations (2, 5). There is evidence for RvE1 stimulation of LXA4 (7), suggest-
ing that SPM may act sequentially or in concert to facilitate wound healing. Clearly, additional studies are required to firmly establish the dynamic changes and interplays in lipid mediator generation during wound healing.

An inherent limitation of this clinical study is that the limited availability of human adipose tissue does not allow one to extrapolate from perivascular and subcutaneous fat tissues to visceral fat and to monitor the dynamic changes in lipid mediator generation during the disease process, and wound healing in particular. Likewise, no clear pictures have emerged regarding potential mechanisms: the authors’ multiple regression analysis did not reveal any relationship between the adipokine/cytokine levels and tissue lipid mediator profile. Intriguingly, body mass index (BMI) did not appear to be associated with SPM levels in PVD patients, indicating that the observed differences in lipid mediator profiles were not simply a consequence of obesity. By contrast, BMI over 35 was accompanied by elevated PGE and PGF2α levels in subcutaneous fat, probably reflecting low-grade chronic inflammation associated with severe obesity. Furthermore, lower LXA4 and RvD2 levels and elevated levels of LTB4 in peri-wound fat from patients with a BMI higher than 25 may represent a potential mechanism for the deleterious effect of obesity on wound healing.

In summary, the novel study by Claria and colleagues (3) identifies important regional differences in the lipid profile in human adipose tissue, which provide a solid starting point for future investigations into the molecular circuits underlying wound healing. A fascinating possibility is harnessing this wealth of information to develop novel therapeutic approaches for the prevention and/or treatment of peripheral vascular disease and other inflammatory pathologies.

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