Commentary

Inflammatory peptides derived from adipose tissue
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Abstract

The low-grade inflammation seen with aging is noted particularly in subjects with the metabolic syndrome of aging. Insulin resistance, obesity/abdominal obesity, and risks for many age-related diseases characterize this common syndrome. It is becoming clear that this increased adipose tissue is not simply a reservoir for excess nutrients, but rather an active and dynamic organ capable of expressing several cytokines and other fat-derived peptides (FDP). Some, but not all, FDP may have a role in development of the metabolic syndrome but there is no evidence that these FDP are causing inflammation directly. We suggest that high levels of inflammatory peptides are markers for obesity/abdominal obesity seen with aging, but some may not necessarily have a causative role in the development of inflammation.

Because bone marrow and adipocytes are derived from the same stem cells, it is not surprising to find so many inflammatory peptides expressed in fat tissue. Many of these are classical inflammatory peptides derived from components of the adipose tissue and all are known also as fat derived peptides (FDP). With aging, there is a linear accumulation of adipose cells and percent of body fat increases. This increased body fat is characterized by increased visceral adiposity [1] and occurs despite the decreased subcutaneous fat and progressive sarcopenia typical of aging [2]. Visceral adiposity has been associated with greater risks for age-related diseases [3]. In addition, fat infiltration typical of aging occurs in many organs including liver and bone marrow. As adipose tissue accumulates throughout the body and in other organs, it is possible that this hyperplastic adipose tissue over expresses FDP.

The metabolic syndrome is a common disorder consisting of a cluster of abnormalities including insulin resistance, dyslipidemia, and hypercoagulability and is associated with increased risk for cancer, Alzheimer's disease, type-II diabetes and atherosclerosis [4]. It is also associated with increased fat mass and increased inflammatory peptides. The obesity epidemic of the rapidly growing aging population makes understanding underlying relationship between adiposity, chronic inflammation and the metabolic syndrome essential.

Increased inflammatory peptides are being studied as possible modifiable markers of the increased risk predictors of disease and possibly the underlying link between obesity and the poor clinical outcomes seen with the metabolic syndrome. More specifically, C-reactive protein (CRP) is the most well established inflammatory cytokine in the clinical setting but there are other inflammatory cytokines including IL-6, leptin, TNF-α, and other (non-cytokine) FDP, such as PAI-1, adiponectin and resistin, which may play a role in the pathogenesis, and/or serve as markers of risk in the metabolic syndrome. The fact that
many of these peptides are derived from adipose tissue leads us to the question of whether adipose tissue itself is
the underlying pathophysiological link between obesity
and the poor clinical outcomes associated with the meta-
bolic syndrome. We will provide a brief overview of some
of the peptides associated with the metabolic syndrome.

Cytokines with a potential role in the metabolic
syndrome
TNFα, leptin, and IL-6 are examples for cytokines that
may have a role in the metabolic syndrome. TNFα, previ-
ously known as lymphotoxin and cachetin, is believed to
be involved in the wasting that occurs during acute and
chronic illness and malignancy. In the basal state TNFα is
directly proportional to fat mass and has been shown to
be involved in the development of insulin resistance [5].
In-vitro studies have demonstrated that TNFα decreases
the insulin receptor tyrosine phosphorylation, and down
regulates several steps in the insulin signaling pathway [6-
9] while neutralizing agents for TNFα have been shown to
improve insulin resistance. [10] Thus, TNFα is not only a
classical cytokine but may be causal in the insulin resistance
of the metabolic syndrome of aging.

Leptin is a peptide derived from adipose tissue and like
other cytokines acts through a cytokine receptor. It is
expressed and secreted in direct proportion to fat mass.
Leptin exerts effect predominantly through receptors in
the hypothalamus but it may also have peripheral actions
[5]. Leptin serves as a marker of energy sufficiency by rap-
idly decreasing during starvation and weight loss. [11]
With obesity, leptin levels are increased in proportion to
fat mass, but its activity to decrease appetite seems
reduced. Leptin appears to have an important role in energy
regulation but no apparent role in development of inflamma-
tion.

IL-6 is another cytokine derived from adipose tissue. Its
expression and circulating levels correlate directly with
obesity, and weight loss will lower circulating levels. Ele-
vation of circulating IL6 is a predictor of the develop-
ment of cardiovascular disease and diabetes [12]. Infusion of
IL6 results in hyperlipidemia, hyperglycemia and insulin
resistance in experimental models. [13] Additionally, IL6
decreases the expression adiponectin, an ‘anti-diabetic’
cytokine. [14] IL-6 plays a role in the development of insulin
resistance and may directly cause induction of CRP.

Other inflammatory cytokines such as IL-1, IL-8, IL18,
Serum Amyloid A, have been shown to be increased with
obesity and may have a yet undetermined role in the syn-
drome. These cytokines are other examples of inflamma-
tory markers which do not have a clear role in the cau-
sation of systemic inflammation.

Non-cytokine Fat Derived Peptides with a role in
the metabolic syndrome
Adiponectin is highly expressed in adipose tissue, and is the
one non-cytokine FDP that is protective from inflamma-
tion. Unlike most FDP, circulating levels are inversely pro-
portional to obesity and therefore tend to be low in
obesity. Adiponectin levels increase with weight loss and
with use of insulin sensitizing drugs. [15] Adiponectin
administration has been shown to improve insulin sensi-
tivity. [16] Low levels of adiponectin have been linked to
inflammatory arthrosclerosis in humans.[17] Animal
models have shown that low adiponectin levels increase
smooth muscle proliferation in response to injury, in-
crease free fatty acids levels and cause insulin resist-
ance.[18] The pro-diabetic and pro-atherogenic effects of
low adiponectin levels seen in the metabolic syndrome
provide a link between inflammation and obesity.

Plasminogen activator inhibitor type-1 (PAI-1) is the primary
inhibitor of fibrinolysis and is highly expressed in adipose
tissue. Levels of PAI-1 are elevated in acute conditions
such as deep venous thrombosis, and chronic conditions
such as obesity, the metabolic syndrome of aging and dia-
betes. PAI-1 levels are correlated with adiposity and signif-
icantly overexpressed in the adipose tissue of obese
compared to lean animals. [19] Levels are decreased by
weight loss and drugs that improve insulin sensitivity
[20]. The relationship of PAI-1 to obesity provides a
potential link between the metabolic syndrome and
hypercoagulabilty.

Angiotesinogen (AGT) is a peptide that is produced in the
liver and in adipose tissue. The strong correlation between
obesity and hypertension implies that adipose tissue may
play a role in blood pressure regulation and in fact there
is a correlation between circulating AGT levels and obe-
sity/hypertension [21]. Animal studies have shown that
overexpression of AGT results in hypertension while
under expression of AGT results in decreased blood pres-
ures [22].

Resistin is a peptide which is elevated in obesity and
appears to play a role in glucose homeostasis in rodents.
In experimental models, resistin induces hepatic insulin
resistance while anti-resistin antibodies have the opposite
effect [23]. In humans, the role of resistin is less clear and
it is not known what role it has glucose homeostasis or
whether it directly relates to adipose tissue mass. The role
of resistin in pathogenesis of inflammation is also
unclear.

Markers of inflammation or markers of obesity?
Low grade inflammation is a predominant feature in the
metabolic syndrome of aging and seems to be linked to
the development of diabetes and poor vascular outcomes.
We have briefly named several cytokines and other FDP that are generally increased with fat mass. Although many of these FDP have a role in metabolic homeostasis, many seem to lack distinct role in inflammatory pathogenesis. While many FDP have roles in vivo metabolism, we suggest that some levels of cytokines are increased because of the hyperplastic characteristic of adipose tissue, and their levels are better serve as marker of adipose tissue hypertrophy, rather than having a causal role in aging. Thus, whether aging is inflammatory state or whether it is a state associated with increased inflammatory marker is subject for further studies.

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