Obesity and related metabolic diseases – Role of chronic inflammation

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ABSTRACT

In today's society with a trend towards westernization, obesity is at its peak affecting around 1 billion people all around the globe. Low-grade inflammation for a prolonged period of time is suggested to be one of the main inducers of the pathogenesis of obesity and its driven by conditions

such as insulin resistance, hypertension, and other cardiovascular diseases. This mini-review summarizes the current knowledge on the mechanistic studies of obesity-associated inflammation and its link to other conditions particularly insulin resistance (IR).

Keywords: Adipocytes, Inflammation, Insulin-Resistance, Lipids, Obesity

INTRODUCTION

The occurrence of obesity and its complications is rapidly increasing and have almost doubled since 1980.¹ There are numerous studies which point out a strong correlation between obesity and insulin resistance, and the key factors recognized for the development of these pathogenesis are over-nutrition and innate immune system.² The inflammatory responses generated during obesity can occur both systemically as well as locally within the affected tissues, which makes obesity-associated inflammation distinct from other types of inflammation.³ Although these inflammatory responses are much smaller in magnitude when compared to conventional inflammation, persistence of such responses for a longer period of time can lead to severe tissue damage.^{2,3} Obesity-induced inflammation also affects the central nervous system and has been shown to affect cognitive functions.⁴ This is even a greater concern in case of obese pregnant women as numerous studies have shown that maternal obesity and its associated inflammation can affect fetal programming and affect the metabolic health of offspring in their childhood and adulthood.⁵

Even though diet and exercise are considered two main strategies to alleviate obesity, but many a times it's hard to implement these lifestyle changes and in some cases they are not sustainable. Therefore, this mini-review is aimed at providing a brief descriptive overview of the causes of obesity induced inflammation and its associated conditions, particularly insulin resistance, in a quest to derive potential therapeutics which can reduce these inflammatory effects.

Causes of obesity-associated inflammation

It is very hard to lay down the precise causes of obesity-associated inflammation, considering different tissues may have different mechanisms. Even though obesity is closely correlated with increased inflammatory markers, the exact reasons behind such relationship is still unknown.² A few of such potential causes or mechanisms are described in the following section.

Gut Inflammation

Certain animal studies have shown that obesity leads to an increase in the gut permeability allowing more lipopolysaccharides (LPS) to penetrate and circulate in the system which are produced from the intestinal bacteria.⁶ LPS when recognized by their respective toll-like receptors (TLRs) can lead to the activation of inflammatory responses, for instance, inflammation activation *via* TLR4 receptors present on adipocytes. This is in conjunction to the fact that many studies have also reported elevated levels of circulating LPS in type-2 diabetes (T2D) patients.⁷ However, activation of inflammation through LPS is mainly systemic and thus increases the amplitude of any existing inflammatory effect rather than activating any tissue specific inflammation itself. This was suggested in a study by Winer *et al.* which described that intestinal immune system can readily influence and affect the systemic immune system, thus leading to pathogenesis of several metabolic disorders associated with obesity.⁸

Hypoxia

Hypoxia is a lack of oxygen state which is developed sometimes by adipocytes during their expansion due to increased oxygen consumption by the cells

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or relatively lesser blood flow to the enlarging tissue. This may activate inflammatory responses in the adipocytes *via* the activation of the *hypoxia inducible factor 1*, *HIF1 gene*. This was confirmed by the fact that inactivation or deletion of the *HIF1 gene* reduced obesity-induced inflammation as a protective mechanism along with improving insulin sensitivity.⁹ A recent study confirmed the role of hypoxia as a causative factor of inflammation by exposing adipose tissues to hypoxic growth conditions, which eventually led to the activation of inflammatory genes.¹⁰

Lipid molecules

Certain lipid molecules, such as lauric acid, found in our diet can serve as activators of the inflammatory pathways. For instance, studies have shown that certain free fatty acids are able to bind to TLR4 and TLR2 receptors indirectly which eventually leads to the activation of inflammatory pathways.⁷ Following their activation, chemokines produced from the specific tissues (such as liver and adipocytes) would attract macrophage infiltration into them leading to further inflammation.

Brain Functions

Hypothalamus in the brain, particularly the ones involved in energy homeostasis regulation and systemic metabolism, are involved in obesity-associated metabolism, as any changes in these areas would lead to the progression of inflammation. The hunger centre located in the hypothalamus regulates our feeding behaviour, and thus it was reported that the inflammation in the hypothalamus is reported to show inflammation, before any of the peripheral tissues inflammation.¹¹

Mechanical stress on adipocytes

The interaction between the extracellular matrix (ECM) and fat cells is very critical as it regulates the expansion and differentiation of the adipose tissues in regards to obesity. When the adipose tissues do not receive enough ECM flexibility for their expansion, they tend to undergo mechanical stress. Lipid overload also results in mechanical stress or stretching to adipocytes. Studies have shown that deletion of MMP14 gene (collagen encoding gene), affected the synthesis and storage of fats.¹²

Activation of macrophages in obese conditions

Under metabolically healthy conditions, the adipose tissues contain numerous immunogenic cells, mainly T lymphocytes, which maintains the integrity of these fat cells. However, during inflammation, these lymphocytes recruit other immunogenic

cells like the mast cells, resident macrophages in an M2 state, through various cytokines. In turn, these immunogenic cells counter the inflammation *via* the production of anti-inflammatory cytokines such as IL-10. On the contrary, during obese conditions, it has been found that the composition of the resident macrophages in adipocytes shift from an M2 polarized state to M1 polarized state, which is a sign of a pro-inflammatory state. This increase in the ratio of M1 to M2 in adipocytes is a unique characteristic of development of obesity and its related conditions such as insulin resistance.¹³ This is also confirmed by animal studies which shows that lean mice have a greater number of M2 polarized resident macrophages, whereas obese mice depicted more of M1 macrophage markers and also led to formation of crown-like structures within the adipocytes. Lean mice also showed a uniformly distributed fat pads compared to obese mice.¹⁴

Mechanisms linking obesity-induced inflammation to Insulin Resistance

Several studies positively correlate the association of inflammation with insulin resistance. For instance, numerous data showed the improvement of insulin sensitivity with the inhibition of NF- κ B or JNK inflammatory pathways.^{7,15-17} Similarly, it has also been shown that Leukotriene B4 produced from the adipose cells can directly reduce the insulin signalling pathways in liver and heart cells.¹⁸ Moreover, in an animal study where the I κ B kinase (*IKK β*) gene was excised using LysMCre-mediated gene deletion (i.e. the NF- κ B pathway was inhibited), it was shown that mice were partially protected from the high fat diet-induced weight changes.¹⁹ On the other hand, another study which used transgenic *Jnk-null* mice were also protected from high fat diet changes, with exposure to saturated fatty acid palmitate, as compared to their wild type mice.²⁰

CONCLUSION

Most of the metabolic syndromes are associated with certain immune dysregulation in the form of inflammation. Although it has been shown that in obesity, the inflammation may not be very intense, however, a prolonged exposure to a low-grade obesity-induced inflammation gives rise to other metabolic conditions such as insulin resistance which eventually leads to T2D. This basically shows that inflammation is a key baseline regulator of all metabolic diseases which still needs a better understanding. However, in order to find suitable and potent therapeutics to treat such metabolic diseases, one must really consider targets for inflammation.

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