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Review Article

Xenoestrogens and Metainflammation: An interplay between Immune System, Metabolism and Obesity

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Obesity is the greatest threat to mankind in twenty first century. It is accompanied with low grade chronic inflammation (metainflammation) which persists in all the tissues involved in energy balance. Obesogens such as xenoestrogens enter into the body and disrupt normal metabolism of cells which are responsible for fat deposition namely adipocytes. The research findings demonstrated that macrophages play a crucial role in metabolic tissues during the onset of obesity. When an intricate balance between metabolism and innate immunity is disturbed, macrophages surrounding adipocytes get activated and converted into pro-inflammatory subtypes. Pro-inflammatory macrophages secret pro-inflammatory cytokines such as Interleukin 6, Tumor Necrosis Factor-α and C- reactive protein. In the present review, an attempt has been made to elucidate the molecular mechanisms involved in xenoestrogen-induced obesity and metainflammation. Further the role of immune system and the involvement of metabolism in the genesis of metainflammation have also been explored briefly.

Introduction

According to the World Heart Federation (WHF) report of 2022, approximately 2.3 billion individuals were suffering due to obesity worldwide. Interestingly, the number of obese people is higher as compared to the underweight in almost every part of the world. As per the currently ongoing trend, approximately 2.7 billion adults i.e. around 33% of the total global population are supposed to be obese by the year 2025.[1] Along with obesity, the cases of other metabolic diseases like type 2 diabetes mellitus and non-alcoholic fatty liver disease (NAFLD) are also rising significantly.[2,3] Therefore, scientists are exploring to find out the intricate relationship among different metabolic diseases as well as to understand the pattern of disease initiation and subsequent complications. In order to decipher this relationship, the research in the last decades has been oriented towards the concept of immunometabolism, an interface between metabolism and immune system. Apparently, it seems that nutrient- (metabolic process) and pathogen-sensing (immune system) systems are working in a mutually exclusive manner in higher organisms. In lower invertebrates such as drosophila, these two systems are not only working intricately but also are located intertwiningly, known as the fat body.[4] The close association between these two consistently working systems gave birth to a new concept called "metainflammation", the term which was first coined by Hotamisligil in year 2006.[5] In most of obese people, the proliferating adipocytes initiate a cascade of low grade systemic inflammation known as metainflammation. If this persists for a longer period, it can propagate deleterious effects to the metabolically active organs such as pancreas, liver and heart.[6,3]

It is undeniable that unhealthy dietary practices and a sedentary lifestyle have been considered as the predominant contributing factors in continuously surging obesity cases. Moreover, an emerging body of scientific literature emphasizes that exposure to different environmental chemicals act in tandem with these factors to exacerbate the incidence of obesity at an alarming degree.[7] For instance, xenoestrogens, a group of chemicals which mimic the natural estrogen synthesized in the body, play a pivotal role in the development of obesity, other metabolic diseases and metainflammation.[8,9] Among the xenoestrogens, BPA is the most abundant and most studied chemical in both humans and experimental

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models.[10,11] Various *in-vivo* studies have shown that pre- and post-natal exposure to Bisphenol A (BPA) increased the body weight of pups and induced permanent obesity in the adult rodents.[12-14] Therefore, it is clear that these xenoestrogens can target the early phases of life leading to the lifelong effects. Being non-biodegradable and highly lipophilic in nature, the xenoestrogens tend to accumulate in the adipose tissue and cause inflammation for a longer period.[15] In the present article, an attempt has been made to provide a critical insight regarding the role of metainflammation in xenoestrogen-induced obesity. Further, the molecular aspects of the existing interface between xenoestrogens, immune system and genesis of metainflammation has also been explored briefly.

Role of Xenoestrogens in Obesity

Xenoestrogen can cause obesity mainly through metabolic disruption.[16,17] The obesogenic actions of BPA have been extensively studied in the *in-vitro* and *in-vivo* models.[16] Ultimately, the mechanisms through which these xenoestrogens exert their metabolic disruption and obesogenic effect, even when the level of exposure is below the No Observed Adverse Effect Level (NOAEL), are being elucidated by different scientific studies. The relationship between the exposure level of xenoestrogens and weight gain forms an inverted "U" shape, curve where the lower exposure level exerts more deleterious effect than the higher exposure level.[18] Pro-opiomelanocortin (POMC) neurons in the hypothalamus restrict food intake while Agouti-Related Peptide (AgRP) and Neuropeptide Y (NPY) do the reverse effect. The experimental *in-vivo* models showed that BPA-exposed mice had POMC neuron innervations and the AgRP and NPY peptides activities were abolished.[19,20] Apart from doing dysbalance in neuronal control, xenoestrogens can alter the carbohydrate metabolism by causing insulin resistance and necrosis of pancreatic β-cells.[21] They also increase the number as well as the size of white adipocytes by elevating triglyceride content, lipoprotein lipase activity and adipogenic transcription factor expression like CCAAT Enhancer Binding Protein-ß (C/EBP-ß).[7,22] Thus, xenoestrogens perturb the intricate balance between the neuronal control and metabolism of the body and cause excess weight gain as well as obesity.[16]

Xenoestrogens as a Causative Factor for Metainflammation

Xenoestrogens are compounds which have an ability to interfere with the natural hormones which are accountable for the regulation of various physiological functions such as development, behavior, fertility as well as maintaining the homeostasis in the body.[23] The matter of concern is that there are several xenoestrogens which are lipophilic in nature. As Body Mass Index (BMI) increases, these lipophilic molecules accumulate in the adipose tissue. They are non-biodegradable; therefore their concentration tends to increase with time and further continuous exposure is a subject of concern.[24] Basically, there are two types of xenoestrogens: natural (phytoestrogens) and synthetic[23], however some authors do not consider natural ones in the list of xenoestrogens.[25,26] Among the synthetic xenoestrogens, BPA is the most abundant in use; whereas isoflavones form the most important group of phytoestrogens.[27] Although, isoflavones exhibit antioxidant, anticancer, antimicrobial and anti-inflammatory properties, some of them like soy isoflavones are also reported to cause obesity and other metabolic disorders.[28,29] Both of them imitate the action of estrogen and alter the metabolic processes in the body. These are capable to upregulate different transcription factors like Peroxisome Proliferator-Activated Receptor (PPARγ), C/EBP and Nuclear Factor Erythroid 2-related Factor 2 (Nrf2), which can ultimately lead to the induction of obesity and associated metainflammation.[14] Table 1 depicts some of the important xenoestrogens, their sources along with their role in obesity and metainflammation.

Many of xenoestrogens cause metainflammation in a similar way like BPA does. BPA significantly increased the expression of several genes involved in adipogenesis and lipid accumulation, including C/EBPα, C/EBPβ, PPARγ, Fatty Acid Synthetase (FASN) and Sterol Regulatory Element Binding Protein1c (SREBP1c). The up-regulation of these adipogenic transcription factors and enzymes are reported to be involved in the development of metainflammation.[30-32] BPA has an ability to interact with Nuclear Receptors (NR) including Retinoid X Receptor (RXR), PPARγ, Estrogen Receptors (ER), Thyroid Receptors (TR) and Glucocorticoid Receptors (GR), as a result of which it can induce differentiation of adipocytes and lipid accumulation.[33] BPA can also activate classical transduction pathways of ERα and ERβ, which can further reduce adiponectin secretion and increase the proliferation of adipocytes.[34] Organochlorines like Dichlorodiphenyltrichloroethane (DDT) and endosulfan increase the expression of Aryl Hydrocarbon Receptor (AHR) transcription factor, which has the potential to elevate the production of the aromatase, a CYP450 mediated enzyme.[35,36] Aromatase, in turn, converts androgen to estrogen which upregulates the PPAR and c/EBP transcription factors.[36] PPAR and ER family has been reported to correlate the different molecular

pathways involved in the process of metainflammation.[5] Males are more prone to metainflammation and related metabolic diseases as compared to age-matched pre-menopausal females.[37] This type of difference in susceptibility is due to the presence of estrogen, which plays a protective role in pre-menopausal females. Further, post-menopausal females develop more metabolic disorders than age-matched males.[38]

Metainflammation and Immune System: The Connecting Link

Among the immune cells, macrophages significantly contribute to the obesity-induced systemic inflammation. Macrophages have an ability to quickly sense their microenvironment and change their metabolic profile as well as express a wide variety of inflammatory markers.[44] Under the stressful conditions, macrophages are polarized into pro-inflammatory macrophages (M1 subtype), which mainly secretes pro-inflammatory cytokines. Once the stress is over, another type of macrophages (M2 subtype) get activated and play a crucial role in tissue repairing.[45] Interestingly, M2 macrophages utilize fatty acids as the energy source and produce ATP through β-oxidation and oxidative phosphorylation, which is more time consuming. Conversely, M1 macrophages quickly undergo aerobic glycolysis.[46] Macrophages during metainflammation reportedly behave like M1 macrophages to a great extent.[47] These metabolically activated macrophages express low levels of CD206 (overexpressed in macrophages of non-obese animals) and elevated the levels of CD11c, CD36, Macrophage Scavenger Receptor 1 (MSR1), ATP-binding cassette A1 (ABCA1), adipose differentiation-related protein such as Perilipin-2.[48,46,49] Various types of immune cells in the adipose tissue can affect the shift in macrophage polarization. For instance, neutrophils induce this change by using protease elastase, T-lymphocytes by using interferon-γ, natural killer cells induce polarization by TNF-α and MCP1 and B cells contribute by producing IgG antibodies.[50,47] Macrophages expressing CD11c have been linked to insulin resistance and are located in the crown-like structures, which encircle necrotic adipocytes to eliminate them through a process called exophagy.[46] This process results in the uptake of FFA and lipids by macrophages and the formation of foam cells.[51] In summary, obesity induces some changes in the phenotype and behaviour of macrophages which contribute greatly to the overactivation of innate immunity system of our body leading to the initiation of low grade systemic inflammation.

Obesity and Metainflammation: The Molecular Basis

Lipids are involved in the coordinated regulation of metabolic, inflammatory and innate immune processes. The quest for elucidating the molecular signaling involved in metainflammation started around a decade ago when researchers discovered high levels of Tumor Necrosis Factor-α (TNF-α) in the adipose tissue of obese mice. This finding established a clear connection between obesity and chronic inflammation in the experimental mice model.[52] Later, it was established that TNF-α is not released by adipocytes but rather by the macrophages which surround them.[53] TNF-α is a marker of local as well as systemic inflammation, therefore high chances of crosstalk existed between adipocytes and immune system under obese condition.[54,55] According to literature, Endoplasmic Reticulum (ER) can serve as a common target and in fact, it is considered that ER begins the inflammatory cascade in the metainflammation process.[5,56]

In obesity, the elevated levels of Free Fatty Acid (FFA) in the adipocytes increase ER stress which can further activate a number of inter-connected pathways.[57] FFA stimulates the unfolded protein response which is mediated by nutrient fluctuations, hypoxia and the presence of different toxins. This, in turn, generates additional molecular targets such as Activating Transcription Factor 6 (ATF-6), Inositol-Requiring Enzyme Type 1 (IRE1) and Protein Kinase R-like Endoplasmic Reticulum Kinase (PERK), which can further lead to metainflammation.[58,59] It has been reported that ATF-6 increases stress to Golgi body, IRE1 stimulates the lipid droplet formation and PERK binds with PPAR and C/EBP proteins.[60] These three phenomena can increase the oxidative stress in the system and activate Jun N-terminal Kinase (JNK) and IκB Kinase Complex (IKK) factors to cause inflammation and necrosis of adipocytes.[61] Additionally, FFA directly upregulates the expression of PPAR, C/EBP and Nrf2 as depicted in the figure 1. All of these mediators alter the expression of IL-6 and TNF-α which can further stimulate monocyte to macrophage activation. The macrophages also produce IL-6 and TNF-α which also help to initiate the vicious cycle of inflammation.[59]

The leakage of calcium (Ca^{2+}) ions from the outer membrane of ER is another phenomenon which takes place under ER stress. The excess of Ca^{2+} ions are responsible for the mitochondrial damage and secretion of cytochrome-c. This further leads to apoptosis by binding with the Apoptotic Protease Activating Factor-1 (Apaf-1).[62] Both ER stress and mitochondrial damage increase the Reactive Oxygen

Species (ROS) levels which in turn activate JNK and IKK. Both JNK and IKK up-regulate the Monocyte Chemoattractant Protein-1 (MCP-1), IL6 and TNF-α expression but decrease the production of adiponectin, a cytokine produced exclusively by the adipocytes.[63] Reduction in the adiponectin level is also accomplished by GPR30, a G-protein coupled receptor involved in the production of anti-inflammatory cytokines like IL10. Estrogen can have a rapid non-genomic response via GPR30. The GPR30 knockout mice have reportedly exhibited elevated levels of pro-inflammatory cytokines and low adiponectin levels in their circulation.[64] The reduced production of adiponectin and increased production of pro-inflammatory cytokines block the action of Insulin Receptor Substrate (IRS), resulting in the insulin resistance in adipocytes. Insulin receptor via mTORC1-Egr1-ATGL pathway ameliorates the degradation of triglyceride into FFA which increases the size of lipid droplet.[65] Due to large lipid droplets, ER tends to synthesize more proteins to package the enlarged lipid droplets and this phenomenon is responsible for the excessive ER stress.[66] From the existing literature, it is clearly evident that the pathophysiology of metainflammation relies on a complex intertwined pathways involving the metabolic and immune system, which start with ER stress and then progress to other cell-organelles leading to the production of pro-inflammatory cytokines. The purinergic system, specifically the metabolites ATP and adenosine, plays a significant role in the development of metainflammation.[67] Adenosine exhibits anti-inflammatory properties by inhibiting Th1-polarizing responses and promoting the production of anti-inflammatory cytokines and Th2-polarizing responses. On the other hand, ATP, particularly at high extracellular concentrations, contributes to inflammation and cell death.[68,69] In metainflammation, there is a decrease in adenosine levels and a significant increase in ATP levels.[69]

Metabolic Considerations in Metainflammation: Role of Pancreas and Liver

In the context of metainflammation, the pancreas and liver are primarily affected. In the pancreas, metainflammation is associated with two main inflammatory pathways, JNK-AP-1 and IKK-NF-κB, which are connected to IRE-1 and PERK activity during ER stress.[70] These pathways involve interactions between IRE-1 and JNK activation through TNF receptor-associated factor 2 (TRAF2), as well as the association of IRE-1 and PERK activation with the IKK-NF-κB pathway. The activation of IRE-1 and PERK are also associated with the IKK-NF-κB pathway, but through distinct mechanisms. IRE-1 interacts with IKK-ß through TRAF2, whereas PERK activation leads to the degradation of IκB, thereby facilitating NF-κB activity.[71,72] In the liver, metainflammation occurs due to the entry of excessive amounts of free fatty acids (FFA) from necrotic adipose tissue, leading to lipid accumulation in hepatocytes and induce lipotoxicity.[73,74] The liver, like adipose tissue, has resident macrophages called Kupffer cells, and the interaction between hepatocytes and Kupffer cells follows a similar pattern as in adipose tissue. As the liver is crucial for carbohydrate and fat metabolism and relies on insulin, the excess lipid accumulation results in insulin resistance and the production of pro-inflammatory cytokines, disrupting the metabolic regulation.[75,76]

Future perspectives

The purinergic system is a crucial modulator of metainflammation and its role has been investigated in the aetiology of osteoarthritis.[67] The exploration of the role of purinergic system mediated metainflammation in metabolic disorders might open up a new therapeutic avenue for the disease. The relationship between metabolism and inflammation via epigenetic regulation of gene expression is another area which needs more research and may eventually lead to a potential clinical intervention strategy. Recent research suggests that lysine acetylation of both histone and non-histone proteins cause alterations in energy metabolism during chronic inflammation.[77] Therefore, by regulating the expression of pro- and anti-inflammatory mediators, deacetylase inhibitors or activators may be further strategies to prevent macrophage-induced metainflammation. Despite the significant progress made over the past few decades, many concerns regarding the processes of macrophage polarisation and metainflammation remains unanswered. The interaction between macrophages and their milieu is a complicated and dynamic process due to the heterogeneous and versatile character of macrophages. At present the understanding of these interactions in *in-vivo* conditions are limited. These issues can be addressed through the incorporation of new technology, such as computational biological methods for better understanding and interpretation.

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