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REVIEW

Metaflammatory responses during obesity: Pathomechanism and treatment

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Summary Obesity induced inflammation acts as a reflex produced due to altered metabolic homeostasis in accordance to the nutrient overload on the metabolic cells. It involves up-regulation of the genes encoding for cytokines, chemokines and other inflammatory mediators through activated transcription factors — nuclear factor-kB, activator protein-1, nuclear factor of activated T cells and signal transducer and activator of transcription 3. These execute macromolecular innate immune cell sensor — inflammasome to activate caspase-1 pathway resulting in proteolytic maturation. Secretion of pro-inflammatory cytokines including TNF-α, IL-6, CRP, IL-1β, etc. from the M1 macrophages of white adipose tissue is increased, whereas there occurs a steep decline in the production of anti-inflammatory cytokines like IL-10, IL-Ra, adiponectin. Not only the adipose tissue, but also the immune cells, liver, brain, muscles and pancreas suffers from the inflammatory insult during obese condition and are exaggeratedly affected. The inflammatory kinases like JNK and IKK apart from inhibiting insulin action and glucose uptake, down-regulate transcriptional process resulting in increased expression of pro-inflammatory cytokines. Macrophage-like Kupffer cells initiate the inflammatory process in the liver preceding the inflammatory signals produced by the white adipose tissue which may further lead to hepatic-necro-inflammation. The muscle-fibre is affected by the cytokines and therefore results in decreased glycogen synthesis. The triggered hypothalamic—pituitary—adrenal axis further affects the expression of inflammatory

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cytokines thus altering insulin homeostasis and initiating glucose intolerance. Anti-inflammatory treatment so as to curb the severity of inflammatory responses includes administration of synthetic drugs to target the actual inflammatory molecules and various therapeutic interventions.

Contents

Obesity induced inflammation

Obesity is one of the major health hazards marked by excessive body fat accumulation and a body mass index (BMI) exceeding 30 kg/m^2 [1,2]. It is escalating prevalently among increasing number of people with a present count of more than 500 million having high risk of morbidity and death; hence creating ample of societal concern. Since 1990s, this dramatic increase depicts the need for effective interventions to be implemented during early years of life [3]. Excess consumption of nutrients during obese condition triggers the specialized metabolic cells that sustains the insult and initiates the inflammatory process thereby damaging and hampering the metabolic homeostasis. Not only the adipose tissue; but also liver, pancreas, brain and probably muscles experience inflammatory exposure during obese conditions thus producing metaflammatory responses [4,5]. Obesity has been shown to be associated with increased risk of chronic inflammatory and metabolic diseases including type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, coronary heart disease (CHD) etc. that may initiate right from childhood [6].

Altered gene expression during obesity

Inflammation is an exaggerated response of the body towards nutrient overload on the metabolic cells. Obesity induced inflammatory mechanism that renders tissue repair firstly involves up-regulation of the genes encoding for cytokines, chemokines and other inflammatory mediators through activated transcription factors — nuclear factor-kB (NF-kB), activator protein-1 (AP-1), nuclear factor of activated T cells (NFAT) and signal transducer and activator of transcription 3 (STAT 3) [7,8]. Further, inflammasome — a macromolecular innate immune cell sensor activates caspase-1 pathway resulting in proteolytic maturation thereby secreting pro-inflammatory cytokines through the conversion of pro IL-1β to activated