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Leptin inhibitors from fungal endophytes (LIFEs): Will be novel therapeutic drugs for obesity and its associated immune mediated diseases

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ABSTRACT

Treatment of obesity and its associated immune mediated diseases is challenging due to impaired function of leptin system. Thus leptin is providing an interesting target for therapeutic intervention. Leptin, an adipose tissue-derived adipokine, displays a variety of immune functions, and regulate both innate and adaptive immune responses. The increased secretion of leptin (hyperleptinemia) and production of proinflammatory cytokines has been implicated in the pathogenesis of obesity-related immune diseases such as diabetes mellitus, hypertension, atherosclerosis, cancer, systemic lupus erythematosus, rheumatoid arthritis, crohn's disease and multiple sclerosis. These disorders are managed through antibiotics and by cytokines replacement. However, the effectiveness of cytokines coupled to the complexity of the cytokine network leads to severe side-effects, which can still occur after careful preclinical evaluation. In addition, synthetic immunotherapeutics carries a degree of risk, is time-consuming and expensive. Hence, the complexity of existing therapy and adverse effects emphasizes the need of an alternative approach for the management of immune dysfunction associated with obesity and its related diseases. For the aforementioned diseases that are related to leptin overabundance, new drugs blocking leptin signaling need to be generated. The research on the discovery of clinically important novel compounds from natural source is expanding due to their safety and no side effect. The fungal endophytes are the microbes that colonize internal tissue of plants without causing negative effects to the host. They produce plethora of substances of potential use to modern medicinal and pharmaceutical industry. The increasing body of evidence associated with application of bioactive metabolites derived from fungal endophytes in diverse disease states merits its use as therapeutic drugs. In particular, the saponins have been extensively proved to modulate the immune system, which has raised a significant interest in their potential as immunomodulators. Thus, our hypothesis is that the saponins derived from fungal endophytes can be explored as clinical applicable leptin inhibitors for treating immune mediated diseases.

Introduction

The healthy immune system is crucial for survival of human beings. In general, the immune system requires a proper energy balance for its physiological functions [1]. Sometimes, immune system functions abnormally due to disorders and deficiencies which lead to the immune related/mediated diseases [2]. Recently, the interlink between obesity and immunity have been reported by several researchers and identified obesity as predisposing factor for diabetes mellitus, hypertension, atherosclerosis, cancer, and autoimmune diseases namely systemic lupus erythematosus [3], rheumatoid arthritis, crohn's disease and multiple sclerosis [4]. Hence, the identification of the mechanistic links between obesity and immune modulation progression is emerging as a topic of widespread interest. Recently, several groups have addressed that

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hyperleptinemia may play a role in the immune-pathophysiology of obesity and obesity-related immune diseases [5].

Leptin is an adipocyte-derived protein hormone which has been recognized as a key factor in regulating a wide range of biological responses including energy homeostasis, neuroendocrine function and other physiological functions [6]. It plays a crucial role in the regulation of immune functions. Moreover, it is also present within both primary lymphatic and secondary lymphatic organs [7,8]. The structure of leptin is similar to that of cytokine with a four α helix bundle motif that are common the IL-6 cytokine family [9]. Furthermore, the functional leptin receptor shows sequence homology with the receptor for IL-6, leucocyte inhibitory factor and granulocyte colony-stimulating factor. This receptor has been identified in immune cells of both humans and animals. Most importantly, it is involved in the downstream signal transduction pathways characteristic of a cytokine family and lacks intrinsic tyrosine kinase activity [10,11]. Thus, the cytokine-like aspects of leptin is implicative of its function in regulating immune response [6]. In fact, distinctive role of leptin on the immune system is its action as a proinflammatory cytokine. Recently, leptin is recognized as the immuno-stimulator which regulates both the cellular and humoral immunity of innate and adaptive immune responses in obesity and other leptin mediated immune diseases. There is increasing evidence that plasma leptin concentrations are elevated in obese subjects suggesting that leptin is involved in the pathogenesis of obesity and obesity related immune disorders/diseases such as hypertension, atherosclerosis, cancer and autoimmune diseases [12].

Taking into consideration the pathologies associated with the overabundance circulating leptin on immune system, it could be suggested that the control of the amount of bioavailable leptin might be a good way to avoid undesired leptin actions in aforementioned diseases. As no specific drugs are available currently, the leptin mediated immune disorders and/or diseases are managed through antibiotics and by cytokines replacement. Moreover, the long run usage results in various side effects and metabolical disturbances [13]. Hence the natural immunomodulatory drugs that affect leptin are attracting the global attention. An immunomodulator can regulate the disturbed immune system by activating the innate and adaptive immune response. Hence there is a need to search for an alternate source.

In this context, fungal endophytes have become an important source of new pharmacologically active metabolites as evidenced by the chemical diversity of their secondary metabolites. Global efforts to discover novel biologically active compounds from fungal endophytes have increased in the last decade [14,15]. Bioactive compounds with antifungal [16], cytotoxic [17], antioxidant [18], antiviral and antimalarial [19] properties have been found from fungal endophytes.

The reports on the isolation and characterization of immunemodulating bioactive compounds from fungal endophytes are scanty. Recently, innovative penstyrylpyrone compound isolated from fungal endophyte *Penicillium* sp. JF-55 displayed its activity on the pro-inflammatory mediators and NF-κB DNA binding which further associated with the HO-1 expression. The transcription factor NF-κB has been implicated in the regulation of many genes that encode for mediators of immune responses [20]. Although there are no leptin inhibitors drugs derived from endophytes, it is clear that the fungal endophytes represents a potential source of bioactive molecules that should be explored more thoroughly.

Thus, we hypothesize that bioactive compounds from fungal endophytes are a potential target for developing inhibitors against leptin in immune mediated diseases. Understanding the different mechanisms that regulate leptin over dominance in obesity and obesity associated immune diseases/disorders would provide insights about connection link between leptin and immunemodulation and enable us to develop strategies for leptin inhibitors. The fundamental rationale behind this approach can be summarized as follows: (i) to identify fungal endophyte derived therapeutic molecules that inhibit leptin expression (ii) to explore to develop potential bioactive inhibitors from fungal endophytes which will prevent the elevated levels of circulating leptin and that are less toxic and safe, (iii) to identify the immune regulating mechanism of action of leptin inhibitors derived from fungal endophytes (LIFEs).

Hypotheses

We propose that the saponins derived from fungal endophytes have the protective effects on obesity and its associated leptin related immune diseases and/or disorders through the modulation of activated leptin-nuclear factor-kappaB (NF-κB) signaling.

Evaluation of the hypotheses

The current immunomodulators for the prevention and recovery of immune related diseases are based on secondary metabolites of plants. Recently, several studies have led to the discovery of important plant secondary metabolites from endophytic fungi thus raising the prospect of using such organisms as alternative sources of these metabolites. There are evidences that the saponins (triterpenoid and steroidal glycosides) are promising bioactive metabolites with immunomodulating activity. Furthermore, many saponins have been shown to inhibit NF-κB, a key player in the regulation of immune response. Recent studies indicated that leptin has direct action on NF-κB signaling via JAK-2 (janus kinase-2) pathway that involves insulin receptor substrate1 (IRS1), phosphatidylinositol 3-kinases (PI3K), 3-phosphoinositide dependent protein kinase (PDK), protein kinase2 (AKT2), I kappa B kinase (IKK) and (IκB). The activation of NF-κB signaling plays a central role in the regulation of adaptive and innate and immune responses through stimulation of cytokines and adhesion molecules which are critical elements involved in the regulation of immune responses (Fig. 1). Thus it is conceivable that inhibition of leptin in NF-κB signaling through JAK-2 pathway may present a promising target in immune therapy. Accordingly it could be hypothesized that saponins derived from fungal endophytes will be a potential new candidate of therapeutic importance against leptin mediated immune dysfunction in obesity and its associated diseases.

Testing the hypotheses

The isolation of fungal endophytes is an important step for detailed studies on screening for novel bioactive secondary metabolites with therapeutic potential. Generally, the isolation process of fungal endophytes inside tissues of medicinal plants include (1) removal of major epiphytes, debris and soil particles from the plant tissue by thorough washing under tap water, (2) employing different protocols for the surface sterilization of plant tissue to kill any epiphytes on the surface of host [21], (3) placing of pieces of plant tissue on different media such as potato dextrose agar, malt extract agar and water agar etc., for the isolation of fungal endophytes growing plant segments, (4) optimization of incubation and cultural conditions for purification and sporulation of fungal endophytes, (5) identification of the fungal endophytes based on their morphological characteristics and 18S rRNA (ribosomal ribonucleic acid) sequence analysis [22]. It is highly probable that more number of isolates do not sporulate, although various methods to promote sporulation are employed [23]. 18S rRNA molecular sequencing technique, therefore, has been successfully