New insights into growth hormone’s actions on the macrophage: implications for non-growth-related actions of growth hormone

PA Kumar1*, RK Menon2,3

Abstract
Introduction
Growth hormone, besides being essential for post-natal growth in mammals, affects the metabolism of fat, protein and carbohydrates. At cellular level, the pleiotropic actions of growth hormone are due to its interaction with growth hormone receptor, followed by activation of the janus kinase 2–signal transducers and activators of transcription signalling cascade. The effects of growth hormone have been most intensely investigated in tissues such as liver, bone, muscle and adipocytes, in which growth hormone receptor expression is abundant, and are thus considered canonical targets of growth hormone action. However, recent studies on biological effects and physiological relevance of growth hormone action in non-canonical targets such as blastocysts, cardiomocytes, colonic epithelium, glomerular podocytes and macrophages argue the importance of non-growth-related functions of growth hormone. In this review, we discuss immunomodulatory and metabolic effects of growth hormone on the macrophages. This review also highlights the role of growth hormone on macrophage migration, alternative activation and paracrine effect on adipocyte differentiation.

Conclusion
As we expand our knowledge about the role of growth hormone on regulating the components of immune system and metabolism, it may be possible to exploit the new information to enhance host resistance to infection, improve sensitivity to insulin and prevent atherosclerosis in conditions such as acquired immunodeficiency syndrome, short bowel syndrome, Prader-Willi and lipodystrophy syndromes.

Introduction
Since from the discovery of growth-promoting substances in anterior pituitary gland extract by Evans and Long in 1921, the subsequent isolation of the growth hormone (GH) from bovine pituitaries by Evans and Li in 1944, and the successful treatment of a patient with short stature using human GH in 1958, it has become increasingly evident that GH is the central endocrine regulator of postnatal growth. The human GH gene family composes five closely related genes: GH-N (normal gene), GH-V (variant gene), CS-like gene, CS-A and CS-B genes. The GH-N gene encodes the predominant form of GH that is secreted from the pituitary gland, while GH-V encodes a variant of the hormone, which is expressed by the human placenta. The human GH gene encodes a 217-amino acid precursor protein, which upon proteolytic cleavage of the signal peptide, yields a mature single-chain polypeptide of 191 amino acids with a molecular mass of 22 kDa. GH is synthesised and secreted by the somatotrophs of the anterior pituitary gland under the control of neuronal, hormonal and metabolic factors, including blood glucose levels, exercise, sex hormones, glucocorticoids and thyroid hormone.

At the cellular level, the pleiotropic action of GH is elicited by its interaction with the GH receptor (GHR). GHR belongs to class I cytokine receptor superfamily that includes receptors for PRL, leptin and interleukins. The predicted molecular mass of GH is ~70 kDa. An initiating event in this interaction is the activation of janus kinase 2 (JAK2), a GH-associated tyrosine kinase. According to the original model, a single molecule of GH sequentially binds to two GHRs to induce dimer formation, which then increases the affinity of each GHR for JAK2. However, this original concept was revised recently by a study, which indicates GHRs either exist as a dimer2 or as a heterodimer with the prolactin receptor3 and that GH binding brings about a conformational change in the dimer that is important for the post-receptor signalling cascade, including activation of JAK2. Activated JAK2 phosphorylates itself and also the tyrosine residues in the cytoplasmic domain of GHR. These phosphotyrosines are thought to form high-affinity binding sites that recruit a variety of signalling proteins containing phosphotyrosine-binding domains, including signal transducers and activators of transcription (STAT) family proteins. The activated GHR-JAK2 complex can phosphorylate at least four members of the STAT family (STATs 1, 3, 5A and 5B), leading to their dimerisation, nuclear translocation and activation of transcription. Another pathway important in GH-regulated gene transcription is the mitogen-activated...
protein (Ras-MAP) kinase pathway. GH and insulin are thought to converge on common signalling pathways, as GH also stimulates the phosphorylation of the insulin receptor substrates 1, 2 and 3. Intracellular regulators that are antagonistic to GH–GHR–JAK2 signalling pathway include a family of cytokine-inducible genes, termed suppressors of cytokine signalling (SOCS). SOCS proteins are believed to inhibit GH signalling by directly binding to JAK2. In addition to the direct effects of GH on target cells, GH also exerts its action by stimulating insulin-like growth factor (IGF-1) secretion. Besides serving as an autocrine mediator of GH action, IGF-1 also regulates GH secretion via negative feedback regulation on the hypothalamus–pituitary axis (Figure 1). The effects of GH were most intensely investigated in tissues such as liver, bone, muscle and adipocytes, in which GHR expression is abundant, and are thus considered as canonical targets of GH action. Recently, the biological relevance of GH action has been investigated in non-canonical targets such as blastocysts, cardiomyocytes, colonic epithelium, neurons, glomerular podocytes and macrophages. These non-canonical tissues have also been shown to express GHR and respond to GH by activating the classical JAK–STAT signalling cascade. In this review, we have attempted to recapitulate canonical functions of GH, and summarise recent progress made in understanding the non-growth-related actions of GH on macrophages. This review emphasises the potential role of GH in augmenting macrophage activation, migration, and modulation of adipocyte differentiation and resistance to insulin action.

Discussion
The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Role of growth hormone on somatic growth
GH is a mitogen and its primary somatic effect is the promotion of longitudinal growth. GHR null (GHR−/−) mice exhibit a 50% decrease in body size4 and GHRH−/− (GH-releasing hormone) mice reach an adult size of 60% compared with that of wild-type littermates5. Hypophysectomised animals also show markedly decreased post-natal growth4. A prevailing topic of interest among endocrinologists is the relative importance and biological significance of direct versus indirect (e.g. via IGF-1) effects of GH. In 1957, Salmon and Daughaday proposed the somatomedin hypothesis, which stated that GH does not exert its growth-promoting effects directly on target tissues, but rather, through an intermediate signalling substance from liver. This intermediate substance was named as somatomedin and eventually identified as IGF-17. Circulating IGF-1 is primarily produced by the liver in response to GH, and is often used as a clinical surrogate marker of GH secretion, as the serum IGF-1 levels are stable through the day and do not exhibit the pulsatility of GH secretion. The somatomedin hypothesis, which is

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Figure 1: Regulation of GH synthesis and secretion. The hypothalamic growth hormone-releasing hormone (GHRH) and somatostatin (SSTN) act on anterior pituitary gland (APG) and elicit an increase or decrease in circulating GH levels, respectively. GH induces hepatic production of insulin-like growth factor (IGF-1), which in turn has growth-promoting and metabolic effects on canonical target tissues such as bone, liver, adipocytes and muscle (original somatomedin hypothesis). GH also exerts direct effect on canonical and non-canonical tissues and induces local production of IGF-1 that further mediates GH actions in these tissues (revised somatomedin hypothesis). IGF-1 acts on the hypothalamus/pituitary to exert feedback inhibition of GH production.
based on the premise that GH action is mediated via hepatic IGF-1, has been subject to intensive revision, as it has become evident that not all growth-promoting effects of GH are mediated by IGF-1. Interestingly, normal growth and development in mice were noticed even in the absence of hepatic IGF-1, despite significantly decreased serum IGF-1 levels\(^8\). Lupu et al.\(^9\) showed strong evidence of the role of both IGF-1 and GH in somatic growth. Using GHR\(^-/-\) and IGF-1\(^-/-\) mice, these investigators estimated that 17% of the postnatal growth can be attributed to processes unrelated to either GH or IGF-1, 35% of the growth is directly associated with GH-independent effects of IGF-1, and 14% to IGF-1-independent actions of GH. In their model, only the remaining 34% of growth is dependent on the actions of GH mediated by IGF-1\(^9\).

Non-growth-related functions of growth hormone

Role of growth hormone in metabolism

The anabolic action of GH in muscle and bone involves the stimulation of protein synthesis and promoting catabolism of fatty acids instead of glucose. Consequently, GH leads to hyperglycaemia and decreases insulin sensitivity; owing to these actions, GH is generally considered to be a diabetogenic hormone. GH promotes lipolysis in adipose tissue and prevents the uptake of fatty acids through inhibition of lipoprotein lipase (LPL) resulting in elevated levels of circulating free fatty acids and glycerol, which is also evidenced by the fact that GH transgenic mice had decreased body fat and developed severe insulin resistance\(^9\). In the liver, GH promotes gluconeogenesis and glycogenolysis and reduces the uptake of glucose. It also promotes lipogenesis, inhibits lipolysis and increases lipid output by the liver. Mice with a liver-specific deletion of the GHR exhibit decreased hepatic triglyceride secretion, insulin resistance and spontaneous hepatic steatosis. In muscle, GH promotes amino acid uptake and protein synthesis. Interestingly, muscle-specific deletion of GHR seems to protect from high-fat diet (HFD)-induced insulin resistance, and this salutary effect might be attributable to decreased diabeticogenic GH action on the muscle. In adipose tissue, GH promotes lipolysis and targeted deletion of GHR in adipocytes leading to doubling of the fat mass, but has no overt effect on glucose homeostasis. GH also seems to play a role in insulin secretion from \(\beta\) cells in the pancreas. Mice with GHR deletion in the \(\beta\)-cells exhibit decreased glucose-stimulated insulin release and decreased \(\beta\)-cell hyperplasia in response to HFD. The complex role of GH in regulating metabolism in various organs has been discussed in another study\(^11\).

Role of growth hormone in inflammation and immunity

The significance of GH in eliciting host immune response is evident from the observation that hypophysectomised rats are more vulnerable to bacterial infections; whereas supplementation of exogenous GH improves immunity in these animals\(^12\). Several different immune cells such as mononuclear leucocytes, monocytes and cells of monocyte lineage synthesise GH and express GHRs, thus making these cells a target of autocrine, paracrine and endocrine actions of GH. GH treatment has been shown to promote monocyte migration, enhance T and B cell development\(^13,14\). In a cohort of patients in the intensive care unit, GH treatment was associated with increased morbidity and mortality; and it was hypothesised that this effect could be due to modulation of immune function\(^15\). Septic shock is associated with high levels of GH and low levels of IGF-1 in circulation, a scenario attributed to a state of GH resistance\(^16\). The cytolytic potential of natural killer cells is also affected by GH. Thus, natural killer cells from GH-deficient children have an intrinsic defect compared with healthy controls as reflected by their failure to respond to interferon (IFN)-\(\gamma\). Administration of GH to animals with hypopituitarism restores several macrophage (M\(\Phi\)) functions relevant to infection and inflammation such as superoxide production, secretion of tumour necrosis factor (TNF)-\(\alpha\) in response to the appropriate stimuli, and improved protection against lethal Listeria monocytogenes and Salmonella typhimurium infections\(^17,18\). Polymorphonuclear neutrophils (PMN) from aged rats exhibit reduced bactericidal activity towards Escherichia coli and offer resistance to low doses of IFN-\(\gamma\). However, these aged rats implanted with a GH-secreting pituitary cell line exhibited enhanced bactericidal activity towards \(E.\) coli and improved responsiveness to IFN-\(\gamma\)\(^19\). This study suggests that IFN-\(\gamma\) and GH synergistically augment superoxide secretion and bactericidal activity by PMN. In aged animals, application of GH or injection of GH-producing tumour cells resulted in the reversal of thymic involution and stimulation of suppressed immune function\(^20\). It has been speculated that reduction of human GH levels during ageing (somatopause) may contribute to the functional impairment of PMN isolated from aged individuals. PMN isolated from patients diagnosed with hypopituitarism showed depressed respiratory burst activity, which was restored by GH administration\(^21\). GH has been shown to promote the secretion of pro-inflammatory cytokines such as interleukin (IL)-1\(\alpha\), IL-6 and TNF-\(\alpha\) in immune cells\(^22\). In contrast, other studies have reported that GH decreases the production of pro-inflammatory cytokines\(^23\). GHR\(^-/-\) mice have increased plasma levels of anti-inflammatory cytokines and decreased levels of pro-inflammatory cytokines. As inflammatory processes are linked to ageing, obesity and insulin resistance, it is possible that the effects of GH on these somatic
processes could be mediated, at least in part, by its actions on the immune system and inflammation.

Macrophages—a novel target of growth hormone action

MΦs are components of the reticuloendothelial system and one of the key mediators of inflammation. These immunocompetent cells are important antigen-presenting cells and are involved in phagocytosis of pathogens, clearing of infected and tumour cells. Activated MΦs have the potential to produce relatively large quantities of reactive oxygen and nitrogen species that are important in combating intracellular microorganisms. MΦs also secrete molecules that have a wide range of biological activity, including numerous growth factors, pro- and anti-inflammatory cytokines, chemotactic agents, metabolites of arachidonic acid, complement components and coagulation factors. GHR is expressed on monocytes and MΦs. GH has been demonstrated to increase the proliferation and alter the morphology of MΦs. Multiple effects of GH on diverse functions of MΦs will be discussed in following sections.

Role of growth hormone as a macrophage-activating factor and mediator of immunity

Innate immune system is the first line of defence against invading organisms, and MΦs are a critical component of this system. MΦs from a host organism infected with a pathogen display enhanced production of microbicidal reactive oxygen intermediates upon stimulation, a phenomenon referred to as priming, which is a critical event in the activation of MΦs to combat pathogens. In 1988, Edwards et al. showed that both native (isolated from pituitary extracts) and recombinant GH (rGH) augment the production of superoxide anion by blood-derived and alveolar MΦs stimulated with opsonised zymosan24, whereas neutralising the antibody to GH significantly blocks the production of superoxide anions from these MΦs. The potential of GH to augment the production of reactive oxygen species was not only confined to MΦs, but also extended to mononuclear phagocytes24. Additional evidence for immunomodulatory effects of GH was obtained from a study in which GH was shown to increase host resistance to S. typhimurium17. Thus, when challenged with S. typhimurium, hypophysectomised mice died and GH supplementation conferred a protective effect against this mortality. In the same study, it was shown that peritoneal MΦs from both normal and hypophysectomised rats exposed to native or rGH are primed for enhanced production of reactive superoxide and hydrogen peroxide. These series of experiments demonstrated that administration of GH results in MΦ activation, similar to that of the classical MΦ-activating factor, IFN-γ. In another study reported that GH enhances the ability of MΦs to combat Pasteurella multocida23. Monocytes isolated from acromegalic patients have been reported to eliminate Mycobacterium avium, better than those of normal donors23. The importance of GH in MΦ priming is also evidenced by a study with hypophysectomised animals which showed ~80% reduction in MΦ secretion of TNF-α following stimulation with lipopolysaccharide. Exposure to GH triples the production of TNF-α by these MΦs from hypophysectomised rats18. It has been reported that the GH-mediated priming of human monocytes to secrete hydrogen peroxide is mediated via GHR or PRLR without involvement of autocrine mediators such as IGF-1 or TNF-α27. GH also augments both MΦs19,22 and neutrophils23 to secrete superoxide radicals in response to chemical modulators such as formyl methionyl leucyl phenylalanine and phorbol myristate acetate. This unique role of GH in promoting host defence mechanisms led to further studies to investigate the molecular mechanisms involving GH and its anti-inflammatory properties. It has been demonstrated that GH directly induces the transcription of inducible nitric oxide synthase (iNOS) and production of NO in murine peritoneal MΦs. Reduction in GH-induced production of NO and transcription of the iNOS gene in MΦs pre-treated with inhibitors of JAK2 (AG490) suggests that the production of NO by GH is mediated via the canonical GH signalling through GHR-JAK2. In a recent study, it was shown that peritoneal MΦs from GH-treated mice presented higher phagocytic capacity than those cells from animals deprived of GH23. These results reinforce the notion that GH acts as a MΦ-activating factor and modulates immune response either directly and/or indirectly.

Effect of growth hormone on macrophage migration

MΦs originate from pluripotent stem cells in the bone marrow, differentiate into circulatory monocytes and emigrate from blood vessels to give rise to a variety of tissue-resident MΦs each with a specified function (Figure 2). Tissue-specific MΦs include Kupffer cells, alveolar MΦs, splenic MΦs, microglia, mesangial cells and osteoclasts. Pro-inflammatory conditions or metabolic or immune stimuli elicit increased recruitment of monocytes to tissue-specific sites, and these recruited MΦs replace resident populations and react with inflammatory and immune stimuli. Migration or chemoattraction is an essential step for immune cells, including MΦs and neutrophils, to infiltrate host tissues and respond to infection. GH has been implicated in the migration of several types of immune cells, including monocytes, resting and activated T cells, and trafficking of CD4+ CD8 thymic emigrants to the subcutaneous lymph nodes13,14,29-31. It has also been shown that stimulation of monocyte receptors by GH induces
monocyte chemotaxis in addition to inducing respiratory burst and cytokine synthesis\textsuperscript{33,34}. The elevation of plasma GH after exogenous administration of rGH enhances random migration of circulating monocytes assayed in a micropore filter assay system. It is noteworthy that in these studies, TNF-α and IL-6 levels did not change after recombinant human GH (rhGH) treatment, suggesting a direct role of GH in stimulating monocyte migration. It has been hypothesised that the reason for older individuals to exhibit decreased immunity and increased susceptibility to infections is in part due to the age-dependent decrease in circulating levels of GH (somatopause). Recently, it has been shown that GH induces both random migration and chemotaxis of primary cultures of peritoneal and bone marrow-derived MΦs\textsuperscript{35}. GH-dependent migration of MΦs is mediated via SH2B1 (SH2 domain-containing adaptor protein). Phosphorylation of tyr (439 and 494) and ser (161 and 165) residues of the β-isofrom of SH2B1 is involved in GH-dependent MΦ migration\textsuperscript{35}.

The state of obesity is characterised by infiltration, accumulation and activation of MΦs in adipose tissue. Abnormal accumulation of MΦs and dissemination of inflammatory cytokines in adipose tissue are implicated in the pathogenesis of metabolic abnormalities associated with obesity including insulin resistance\textsuperscript{36}. The significance of GH action on MΦs in the maintenance of adipose tissue homeostasis was elaborated in our recent study with MΦ-specific GHR knockout (MΦ-GHR-KO) mice\textsuperscript{37}. These mice that lack GHR in MΦs and fed HFD exhibited increased infiltration of MΦs and chronic inflammation in adipose tissue, resulting in insulin resistance and glucose intolerance. The increased inflammation in adipose tissue of MΦ-GHR-KO mice fed with HFD is associated with increased adipose tissue expression of osteopontin (OPN), a critical regulator of obesity-associated adipose tissue inflammation and insulin resistance. These findings suggest a beneficial role of GH in maintenance of normal adipose tissue function via its actions on MΦs. It was recently reported that administration of GH during the pre-weaning period to male rat offspring of dams subjected to under-nutrition ameliorated bone marrow MΦ inflammation\textsuperscript{38}. Bone marrow MΦs from GH-treated adult male rat offspring following maternal under-nutrition displayed markers of alternative (M2) MΦ activation, in contrast to bone marrow MΦs from adult male rat offspring naïve to GH treatment following maternal under-nutrition, which were skewed towards the M1 phenotype\textsuperscript{38}. As maternal under-nutrition is associated with the development of obesity and metabolic complications in the adult offspring, this study...
Role of growth hormone on macrophage-dependent adipocyte differentiation

The adipose tissue normally functions as a reservoir to store fatty acids and promotes appropriate compartmentalisation of nutrients and lipids. Although adipose tissue is largely composed of adipocytes, it also contains a significant amount of other cell types including fibroblasts, MΦs and endothelial cells. All of these cell types appear to be important for the functioning of the adipose tissue and may be responsible for normal behaviour and secretion of certain molecules by adipose tissue. Obese individuals have impaired adipogenesis along with lower levels of circulating GH. As discussed above, obesity is a metabolic perturbation characterised by excessive infiltration of MΦs in adipose tissue. Previously conducted in vitro studies have revealed that a conditioned medium from MΦs that were exposed to GH inhibits the differentiation of 3T3-L1 preadipocytes to adipocytes.

Adipocyte is a major target of action of GH, and GH promotes catecholamine-induced lipolysis, accretion of lean tissue, and decreased accumulation of triglycerides in the adipocyte. Traditionally, these actions of GH are believed to be mediated directly by activating GHR on the adipocyte, which results in increased lipolytic activity and decreased accumulation of triglycerides via inhibition of LPL activity. Recent studies have indicated that in addition to direct effects of GH on adipocytes, GH also regulates adipocyte differentiation by altering the activation of GHR on MΦs resulting in alteration of the cytokine profile of MΦs and subsequently regulates differentiation and functioning of adipocytes. Stimulation of MΦs with GH decreases the inhibitory activity of conditioned medium from MΦs on differentiation of 3T3-L1 preadipocytes. This paracrine effect of GH on adipocyte differentiation is, at least in part, due to decreased expression of IL-1β in GH-treated MΦs. IL-1β is a known inhibitor of adipogenesis and its mRNA and protein were significantly decreased in GH-treated J774A.1 MΦs. Evidence for paracrine effect of GH on adipose tissue is also present in the MΦ-GHR-KO model. Mice devoid of GHR in MΦs when challenged with HFD exhibited increased MΦs infiltration and chronic inflammation in adipose tissue associated with insulin resistance and glucose intolerance. The increased inflammation in adipose tissue of MacGHR KO mice was associated with increased expression of nuclear factor (NF)-κB-dependent OPN, a critical regulator of obesity-associated adipose tissue inflammation and insulin resistance. GH suppresses NF-κB activation and inhibits IL-1β and osteopontin expression. Therefore, GH's actions on MΦ augment adipogenesis under normal conditions and combat chronic inflammation and insulin resistance under obese conditions.

Administration of GH could have salutary effects on DIO-associated chronic inflammation and insulin resistance in humans. A recent study has reported that targeted ablation of GHR expression in adipose tissue of a mouse did not alter glucose metabolism with a normal diet. These results were obtained from mice fed on a normal diet, and it would be of interest to compare the effect of GH action on adipose tissue versus adipose tissue MΦ in HFD-fed conditions.

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The role of growth hormone-dependent alternative activation of macrophages in the modulation of inflammation and insulin resistance

As opposed to a typical acute inflammatory response, which is generally self-limiting with associated inflammatory molecules having short-lived effects, the inflammation associated with obesity is chronic, low-grade, most conspicuous in the adipose tissue and requires continued secretion of pro-inflammatory molecules. Obesity and chronic inflammation are not only correlative but also causative, and obesity is associated with an increased incidence of atherosclerosis, insulin resistance and some types of cancers. Under physiological conditions, the MΦs residing in adipose tissue exhibit a specific phenotype, designated as M2, and perform functions such as tissue remodelling and uptake of particulate matter such as getting rid of apoptotic cells and other cellular debris. These resident MΦs have an anti-inflammatory expression profile characterised by muted expression of IL-1, IL-6, IL-12 and TNF with increased expression of IL-10. Specifically within adipose tissue resident and infiltrating MΦs are known to localise around apoptotic adipocytes to form ‘crown-like’ structures and function to phagocytise lipids and the dead cells. The infiltrating population of MΦs recruited to adipose tissue in obesity exhibits a different phenotype, designated as M1-MΦs. The M1-MΦs are responsible for the secretion of the inflammatory molecules such as IL-1, IL-6, IL-12, IL-23, TNF and display decreased expression of the anti-inflammatory cytokine IL-10. In fact, the M1-MΦs have been identified as the primary source of a number of circulating pro-inflammatory molecules in case of obesity. M1-MΦs are considered as classically activated MΦs, while M2-MΦs are referred to as alternatively activated MΦs. Thus, the MΦs content of adipose tissue is considered to be a critical factor that links obesity to chronic inflammation. The upregulation of inflammatory molecule expression in obesity includes the cytokines TNF-α, IL-6, leptin, IL-1β and monocyte chemoattractant protein 1 (MCP-1). These inflammatory cytokines not only contribute to adipose inflammation, but decrease insulin sensitivity in adipocytes, thus providing a possible mechanism for the insulin resistance associated with obesity and inflammation. The inflammatory state of adipose tissue is much increased in visceral adipose tissue as compared with subcutaneous adipose tissue, with visceral adipose showing increased expression of inflammatory molecules such as TNF-α, IL-6 and MCP-1.

GH has a profound effect on adipose tissue and has been shown to decrease the amount of fat mass and increase the amount of lean mass in mice in a depot-specific manner. Earlier studies have shown that GH has a direct impact on MΦs, altering their morphology and expression profile. This suggests that in addition to having profound, direct effects on adipose tissue, GH may also act indirectly on adipose tissue by altering the expression profile of resident MΦs within the tissue. MΦs infiltration has been observed in wild-type mice depending on the adipose tissue depot. Expression profile of MΦs within subcutaneous adipose tissue is more significantly altered by GH than those of epididymal adipose. Within subcutaneous adipose tissue, GH causes the up-regulation of both M1 and M2 MΦs markers. GH is a positive regulator of the pro-inflammatory molecule MCP-1, which is secreted by both adipose tissue and MΦs and associated with MΦ infiltration into adipose tissue. However, these results are contradicted by another study, which shows that patients with GH deficiency have higher basal levels of the inflammatory molecules TNF-α and IL-6, and these levels return to normal following GH replacement therapy. According to this study, GH decreases inflammation by decreasing the amount of pro-inflammatory molecules secreted by M1-MΦs. However, studies from our laboratory demonstrated that GH treatment of MΦs resulted in decreased expression of the pro-inflammatory molecule IL-1β and a decrease in pNF-κB (Figure 3). pNF-κB regulates the expression of several pro-inflammatory cytokines, including IL-1β, IL-2, TNF-α, and IL-12. These GH-induced alterations in MΦ expression profile could have significant effects on adipose tissue differentiation, such as increasing adipogenesis and decreasing inflammation. GH, besides eliciting its action on adipose tissue via MΦs in a paracrine manner, it can also act directly on adipose tissue via the GHR present on adipocytes, which is out of scope of this review. The effects of GH on augmenting MΦ priming, MΦ migration, lipid metabolism and inflammation are summarised in Figure 4.

Metabolic effects of growth hormone on macrophages

Besides being essential for postnatal linear growth, pituitary GH regulates metabolism of carbohydrates, fats and proteins. GH deficiency is associated with a higher incidence of cardiovascular risk, increased body fat, abnormal levels of serum lipids and lipoproteins that were improved by GH replacement therapy. Patients with hypopituitarism have an increased prevalence of premature atherosclerosis. MΦs collected from GH-deficient patients have increased levels of proatherogenic lipoproteins and increased conversion to foam cells. The atherogenic nature of these MΦs has been attributed to elevated expression and activity of MΦ-secreted LPL. LPL is upregulated in several diseases associated with an increased risk for atherosclerosis. This increased LPL activity of MΦs in GH-deficient subjects...
correlates with increased amount of stored proatherogenic lipoproteins and secretion of free fatty acids and TNF-α, suggesting that MΦs of patients with GH deficiency secrete increased amounts of proatherogenic cytokines and contribute to the increased cardiovascular risk 51. Administration of GH is associated with selective inhibition of adipose tissue LPL activity and provides plausible reason for the observed effect of reduction in adipose tissue mass commonly observed after GH treatment in GH-deficient patients. Human GH therapy has been shown to lower plasma cholesterol levels in patients with hypercholesterolemia 51. Mouse peritoneal MΦs and the J774A.1 MΦ cell line respond to GH with a dose-dependent stimulation of cellular uptake and degradation of LDL and enhanced rate of cholesterol esterification 52, suggesting a role for GH in LDL metabolism. It is interesting to note that GH deficiency was associated with elevated cholesterol-enriched LDL and elevated LPL.

**Conclusion**

The dogma is that major actions of GH are restricted to bone, muscle and adipose tissue. However, recent studies have highlighted the physiological significance of non-growth-related actions of GH on several canonical and non-canonical targets. GH has been shown to augment immunity, wound healing, regulate inflammation, insulin sensitivity and mediate metabolic homeostasis via its endocrine/paracrine action on MΦs. These findings directly impact our understanding of the role of GH in conditions such as adult GH deficiency and Prader-Willi syndrome, in which therapeutic role(s) for the metabolic actions of GH are being evaluated. As we expand our knowledge about the role of GH in regulating the immune system and metabolism, it may be possible to exploit the benefits of GH to enhance host resistance to infection, improve sensitivity to insulin and prevent atherosclerosis in conditions such as acquired immunodeficiency syndrome, short-bowel syndrome, Prader-Willi and lipodystrophy syndromes.

**Abbreviations list**

GH, growth hormone; GHR, growth hormone receptor; HFD, high-fat diet; IGF, insulin-like growth factor; IFN, interferon; IL, interleukin; JAK2, Janus kinase 2; LPL, lipoprotein lipase; MΦ, macrophage; OPN, osteopontin; PMN, polymorphonuclear neutrophil; rGH, recombinant growth hormone; SOCS, suppressors of cytokine signalling; STAT, signal transducers and activators of transcription; TNF, tumour necrosis factor.

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