Therapeutic potential of interleukin-15: a myokine involved in muscle wasting and adiposity

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Since the discovery of IL-15 and its role in T-cell proliferation in 1994, different studies on the effects of the cytokine on metabolic effects have been performed. These studies have mainly been involved with the metabolic pathways involved in lipid and protein metabolism. The present review summarises the metabolic effects of IL-15 at different target tissues and the possibilities and potential for therapeutic interventions based on the cytokine's roles in obesity and wasting.

The role of IL-15 in immune function

Interleukin-15 (IL-15) was first identified as a cytokine when it was observed that the supernatant of the monkey epithelial cell line CV-1/EBNA contained a factor that enhanced antitumour response [1]. IL-15 has a broad range of biological activity which includes: the induction of T-cell proliferation [1,2]; the enhancement of natural killer (NK) cell cytotoxicity; the upregulation of NK-cell-derived cytokines, including γ-interferon, granulocyte/macrophage colony-stimulating factor and tumour necrosis factor-α (TNF-α) [3]; the stimulation of proliferation and differentiation of B cells activated with anti-immunoglobulin M [4] and it may even protect T cells and neutrophils from apoptosis [5,6]. Therefore, IL-15 has similar biological activities to IL-2, though it has no significant primary sequence homology to this particular cytokine. Nevertheless, the biological function of IL-15 is mediated through the β- and γ-chains of the IL-2 receptor [7], which explains the high degree of functional similarity between IL-2 and IL-15. Unlike IL-2, however, which is produced almost exclusively by activated T-cells, the IL-15 gene is not expressed in these cells, but has been detected in placenta, skeletal muscle, kidney, lung and heart [1]. In essence, the concept has emerged that while IL-2 operates as a key modulator of T-cell-dependent adaptive immune responses, IL-15 serves a much broader spectrum bioregulatory role. In addition, the cytokine has structural homology to many four-helix bundle proteins [8]. IL-15 is an immunoregulatory cytokine that exhibits pro-inflammatory activity by acting on a wide variety of cell types. These effects are direct (activating different cell types) and some are indirect (activating the production of other pro-inflammatory cytokines such as IL-18) [9].

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IL-15 and skeletal muscle

Quinn *et al.* [10] have proposed a very important role for IL-15 in skeletal muscle. IL-15 can stimulate differentiated myocytes and muscle fibres to accumulate increased amounts of contractile proteins [10]. In addition, IL-15 stimulates muscle-specific myosin heavy chain accumulation by differentiated myocytes and muscle fibres in culture, suggesting that it may play a role in skeletal muscle fibre growth *in vivo* (Fig. 1). IL-15 also stimulates mouse skeletal myoblast differentiation under certain conditions [11]. Additionally, IL-15 is able to increase myosine accretion in human skeletal muscle cultures (Fig. 1) [12]. Overexpression of IL-15 in mouse C2C12 cells results in a clear muscle hypertrophy; interestingly, this effect of the cytokine is different from the hypertrophic action of insulin-like growth factor-I (IGF-I), because IL-15 induces myotube hypertrophy, yet does not produce stimulation of skeletal myoblast proliferation or differentiation [13]. The action of IL-15 was inferred from the activation of protein synthesis and concomitant inhibition of protein degradation in cultured skeletal muscle cells (Figs 1,2) [13]. With respect to intracellular signalling, very recent observations have demonstrated that the transcription factor PPAR-δ may be involved in the effects of IL-15 on protein synthesis in C2C12 cells [14]. Thus, IL-15 could activate this transcription factor and, in this way, regulate the expression of various genes related to protein and lipid metabolism [15]. Bearing this in mind, chronic IL-15 administration followed by an

 1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2008.10.010

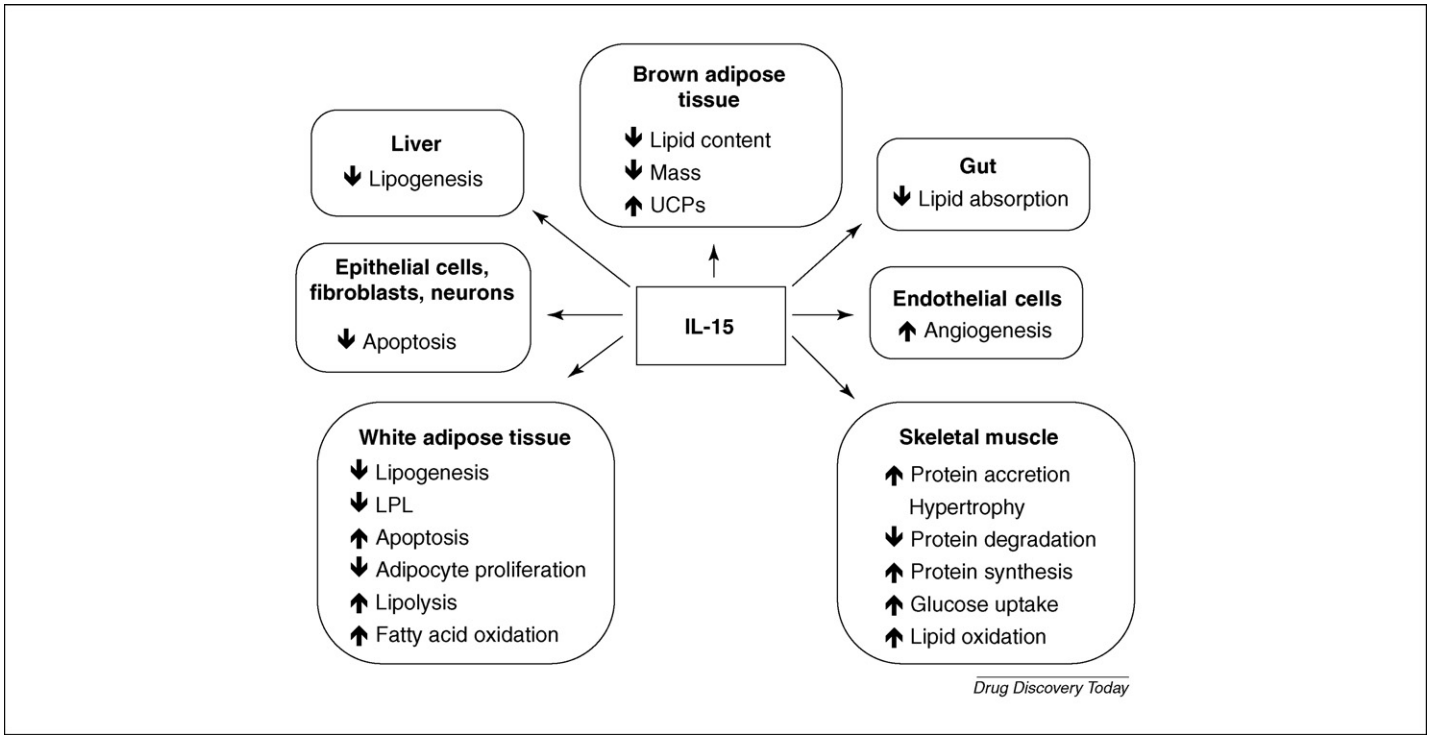

FIGURE 1

IL-15: interorgan metabolic targets. UCPs, uncoupling proteins; LPL, lipoprotein lipase.

intragastric lipid load to experimental animals produced a significant elevation of PPAR-δ mRNA content in both skeletal muscle and liver, suggesting that the proposed actions of the cytokine on lipid metabolism in both tissue targets may be associated with this transcription factor. Interestingly, several investigators suggest that IL-15 may be an important mediator of muscle mass response in relation to resistance exercise training in humans [16,17]. The effects of IL-15 on nitrogen metabolism in skeletal muscle cells,

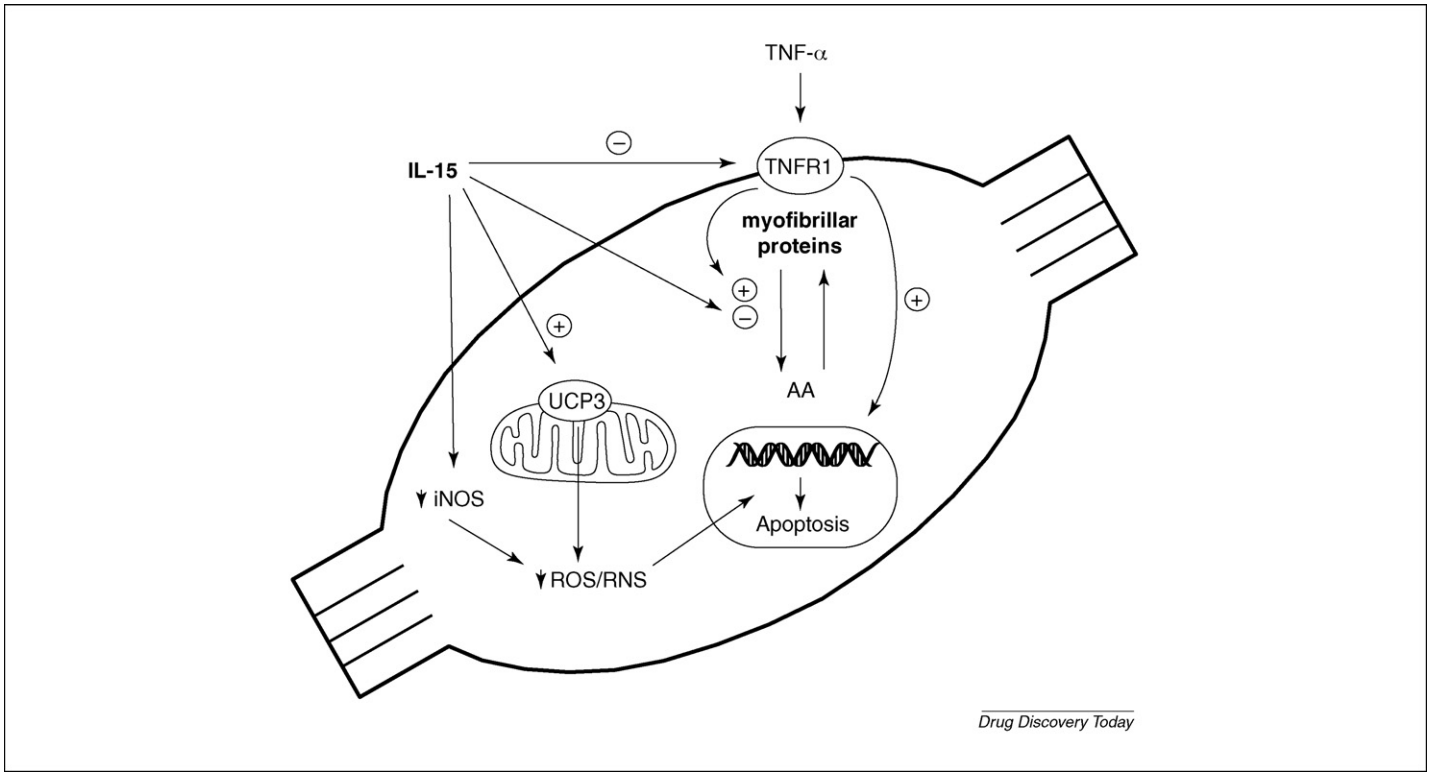

FIGURE 2

Effects of IL-15 on skeletal muscle. TNF, tumour necrosis factor-α; AA, amino acids; ROS, reactive oxygen species; RNS, reactive nitrogen species.

however, seem to be independent of amino acid uptake; indeed, the cytokine seems unable to modulate amino acid uptake whether examined *in vitro* (determined by the uptake and metabolic fate of alanine) or *in vivo* (determined by the uptake of α-aminoisobutyrate, a non-metabolisable structural analogue of alanine) [18]. IL-15, however, does modulate glucose uptake in incubated skeletal muscle and muscle cell cultures, implying that the cytokine may play a role in the inhibition of the development of diabetes, as proposed elsewhere (Fig. 1) [19]. Indeed, *in vivo* administration of IL-15 results in an increase in 2-deoxyglucose uptake in skeletal muscle [19]. In addition, the presence of the cytokine increases GLUT-4 content in muscle cell cultures [19]. It has to be pointed out that skeletal muscle is responsible for cleaning up to 80% or more of glucose load under insulin-stimulated conditions. In addition to promoting changes in carbohydrate oxidation, IL-15 also seems to influence fatty acid oxidation in skeletal muscle, studied in experimental animals by oral administration of exogenous triglyceride in the form of [^{14}C]-triolein [15]. In these animals, IL-15 treatment increases the oxidation of the label, which is strongly associated with enhanced fatty acid oxidation in skeletal muscle. Indeed, additional experiments have demonstrated that IL-15 enhances the rate of palmitate oxidation in C2C12 cells (Fig. 1) [14]. The above observations intended to establish a clear anabolic role for IL-15 skeletal muscle have been confirmed by the observation of the effects of the cytokine in catabolic conditions. From this point of view, during cancer there is a clear muscle wasting condition resulting in an increased rate of protein degradation. This phenomenon contributes to the syndrome known as cachexia (from the greek *kakos* and *hexis*: bad condition). Indeed, the administration of IL-15 to cachectic tumour-bearing animals results in an improvement in the protein wasting process [20].

IL-15 decreases the rate of protein degradation during cancer by interfering with the ATP-ubiquitin-depending proteolytic system [20]. From this point of view, IL-15 has been considered as an 'anticachectic' cytokine, favouring protein accretion in the cachectic muscle. Previous studies have demonstrated that the increased proteolytic rate observed in this catabolic condition is intimately associated with DNA fragmentation and, therefore, apoptosis [21]. As expected, the administration of IL-15 to tumour-bearing animals decreases muscle apoptosis and, therefore, preserves muscle mass [22]. The mechanism involved in this protective role on muscle apoptosis possibly involves activation of uncoupling protein 3 (UCP3) (Fig. 2) [22]. The so-called uncoupling proteins (UCPs) are related to mitochondrial thermogenesis. These proteins uncouple respiration from ATP synthesis by influencing the proton electrochemical gradient across the inner mitochondrial membrane. UCP3 uncouples oxidative phosphorylation at the mitochondrial level [23] and, therefore, decreases the formation of reactive oxygen species (ROS) that seem to be intimately associated with the activation of apoptosis [24]. Our laboratory has demonstrated – at least in experimental animals – that during cancer, TNF-α may be one of the mediators involved in both apoptosis and increased proteolysis in skeletal muscle [25,26]. From this point of view, the fact that the administration of IL-15 to cachectic animals decreases the expression of both tumour necrosis factor alpha receptor I (TNFRI) and tumour necrosis factor alpha receptor II (TNFRII) [22] constitutes an additional mechanism that may explain the protective effects of the cytokine on skeletal muscle under catabolic conditions (Fig. 2). In fact, IL-15 is highly expressed in skeletal muscle under normal healthy conditions, but the levels of mRNA encoding this gene increase during cancer [27], possibly representing a protective mechanism for the deleterious events commented above. No data concerning IL-15 protein content in skeletal muscle are, however, yet available. Future investigations should concentrate on this point. Additional evidence supporting this protein mechanism comes from the work of Alvarez *et al.* who showed that TNF increased IL-15 mRNA content in cultured murine C2C12 myotubes [28]. In pathological conditions other than cancer, IL-15 has also been shown to have a positive influence; thus IL-15 administration improves diaphragm muscle pathology and function in dystrophic *mdx* mice, suggesting that IL-15 could also have a therapeutic role in the treatment of neuromuscular disorders [29]. In other atrophic conditions, such as ageing sarcopaenia and unloading-induced skeletal muscle atrophy, a significant positive interaction was observed with increases in IL-15 mRNA in response to atrophic stimuli that could be an attempt to counteract muscle mass loss in skeletal muscles during ageing [30].

In conclusion, because IL-15 is highly expressed in skeletal muscle and in view of its overall metabolic action, it can reasonably be assumed that it may have promise in the future as a therapeutic approach for wasting diseases.

IL-15 and white adipose tissue: regulation of fat-free mass

The effects of IL-15 on white adipose fat are particularly interesting; the administration of 100 mg/(kg day) to experimental animals resulted in a 33% decrease of white adipose tissue mass, suggesting a clear antiadipogenic role for the cytokine [31]. This effect on white adipose tissue occurs through a dramatic reduction of lipogenesis together with a decreased uptake of VLDL triacylglycerol through lipoprotein lipase (LPL) (Figs 1,3) [31]. Interestingly, IL-15, at least *in vivo*, does not seem to influence the lipolytic rate in this tissue [31]. Conversely, Ajuwon *et al.* have demonstrated that IL-15 was able to increase lipolysis in primary pig adipocytes; therefore, an increase in lipolysis driven by the cytokine cannot be discarded and would certainly contribute to the antiadipogenic effects of IL-15 [32]. The *in vivo* effects of IL-15 do not influence food intake and, therefore, are merely metabolic [31]. Although the influence of IL-15 on white adipose tissue correlated with decreased leptin levels, the lack of effect on food intake has also been observed with different drugs that also deplete adipose tissue, such as oleoyl-oestrone [33] and β3-adrenergic agonists [34]. Similarly, chronic *in vivo* administration of IL-15 resulted in increased oxidation of exogenous [^{14}C]-triolein and decreased incorporation of the tracer into white adipose tissue (Fig. 1) [15]. Skeletal muscle seems to be the tissue responsible for the increased lipid oxidation [15]. Indeed, the presence of the cytokine in incubated EDL muscle with [^{14}C]-palmitic acid increased $^{14}CO_2$ formation by 39% [15]. The effects of IL-15 on adipose tissue have also been examined in two animal models of obesity: in *ob*/*ob* mice, IL-15 inhibited fat deposition, the animals losing ostensibly adipose tissue, while in the Zucker *fa*/*fa* rat no effects of the cytokine were seen in obese animals, whereas the administration of IL-15 promoted the inhibition of fat deposition

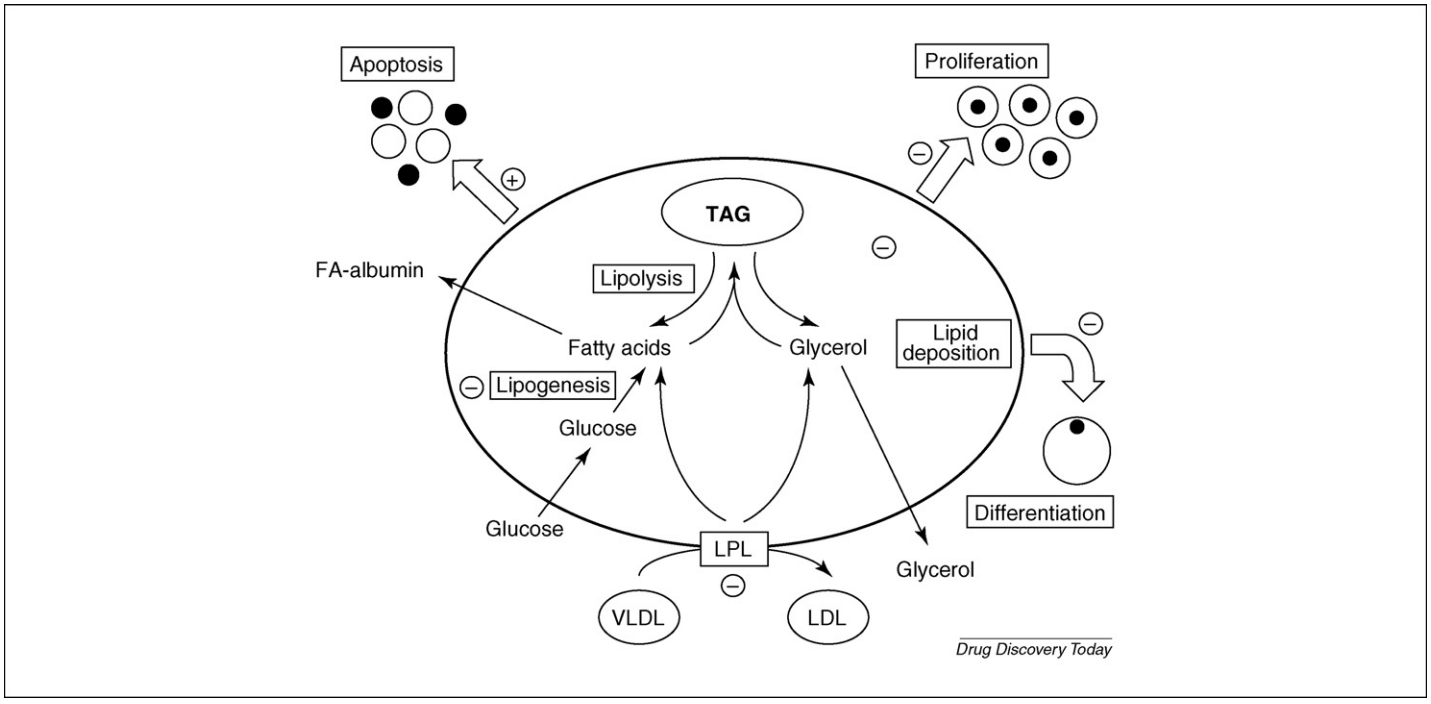

FIGURE 3

Effects of IL-15 on adipose cells. TAG, triacylglycerol; LPL, lipoprotein lipase; LDL, low-density lipoproteins; VLDL, very-low-density lipoproteins; FA, fatty acid.

in control lean rats [35]. This was due to alterations in the gamma (γ) receptor of the cytokine, because its expression was decreased in the obese animals [35]. The effects of IL-15 on adipose tissue seem to be direct, because IL-15 administration inhibited lipid accumulation in differentiating 3T3-L1 preadipocytes and stimulated secretion of the adipocyte-specific hormone adiponectin by differentiated 3T3-L1 adipocytes [36].

In addition to IL-15 having metabolic effects in adipose tissue, recent studies have shown that the cytokine is also able to decrease proliferation of 3T3-L1 pre-adipocytes and to influence, at a later stage, differentiation. These more recently discovered effects of IL-15 seem to be mediated by calcineurin (Fig. 3) [37,38]. Finally, IL-15 has also been shown to increase apoptosis in white adipose cells (Figs 1,3) [37], therefore demonstrating that the antiadipogenic effect of IL-15 relies on many different physiological events. The signalling molecules behind the referred actions of the cytokine on adipose cells are p42/p44 MAPK, which seem to be associated with the decreased proliferation rate induced by IL-15; STAT5, which is related with the actions of IL-15 on differentiation and finally SAPK/JNK, which are related with the increased apoptosis induced by IL-15. In addition, human studies clearly showed a relationship between polymorphisms in the IL-15 receptor genes and metabolic syndrome [39,40]. Altogether, the results presented here reinforce that IL-15 is an important mediator that regulates adipose size and, therefore, the role of the cytokine influencing body weight and obesity deserves additional studies [41]. In fact, recent data suggest that overexpression of IL-15 in skeletal muscle protects against diet-induced obesity [42]. Similarly, Nielsen *et al.* using an IL-15 DNA electrotransfer model suggested that IL-15 may be a regulator of trunk fat mass [8]. The use of IL-15 in clinical practice, however, in particular for the treatment of obesity, rheumatoid arthritis or inflammatory bowel disease, will have to be subject to preliminary studies concerning side effects, because IL-15 is a potent stimulator of T-cells and may, therefore, generate additional systemic inflammation.

IL-15, liver, gut and brown adipose tissue

With respect to the liver, IL-15 dramatically influences lipogenesis; indeed, chronic *in vivo* administration of IL-15 resulted in a 36% decrease in hepatic lipogenesis (Fig. 1) [43]. The decrease in lipogenesis was modulated by a decrease in hepatic concentrations of citrate, one of the main activators of acetyl CoA carboxylase, one of the regulatory enzymes in the lipogenic pathway [43]. The decrease in lipogenesis was accompanied by an increase in fatty acid oxidation, because an increase in CPTI and CPTII in liver tissue was observed following cytokine administration [15]. The net result of these IL-15-induced alterations in liver lipid metabolism is possibly a decrease in triacylglyceride export in the form of VLDL [31]. In agreement with this, in animals treated with IL-15, the concentration of VLDL triacylglycerol was decreased compared with non-treated control animals [31]. On another level, Suzuki *et al.* have described that IL-15 may participate in liver regeneration [44]. In fact, IL-15 expression increased during liver injury and treatment with the cytokine induced a wound-healing-type response in healthy adult mice. The hepatotrophic action of IL-15 seems, however, to be mediated indirectly [44]. It has to be pointed out, however, that in patients with acute hepatic failure there is a significant negative correlation between IL-15 levels and survival, suggesting that high levels of IL-15 result in lower survival [45]. From this point of view, Yonekawa *et al.* suggested that IL-15 overexpression may cause liver injury in humans [45].

Almendro *et al.* showed that the effects of IL-15 on lipid metabolism also involve intestinal absorption (Fig. 1) [41]. Indeed, five hours after intragastric administration of [^{14}C]-triolein to experimental animals, intestinal lipid absorption was significantly

reduced by the cytokine [41]. This observation agrees with the antiadipogenic effect of IL-15, not only lowering lipid uptake by adipose tissue but also influencing the entry of exogenous lipid into the organism. It is well known that brown adipose tissue is involved in non-shivering thermogenesis in humans (neonates) and experimental animals, such as rat and mouse. Interestingly, the administration of IL-15 to experimental animals results in a decrease in brown adipose tissue mass together with a decrease in lipid content, suggesting an activation of the thermogenic process (Fig. 1). This observation is supported by the fact that the cytokine activates both UCP1 and UCP3 gene expression in brown adipose tissue (Fig. 1). In addition, IL-15 also upregulates fatty acid translocase (FAT) and fatty acid transport protein (FATP), proteins involved in fatty acid transport, again suggesting increased fatty acid oxidation and, therefore, thermogenesis. This upregulation is linked with an increase in peroxisome-proliferator-activated receptor-α (PPARα) and peroxisome-proliferator-activated receptor-δ (PPARδ) gene expression, suggesting that these two transcription factors may be involved in the action of IL-15 on brown adipose tissue.

IL-15 and other cell types

Another remarkable effect of IL-15 is increased angiogenesis in endothelial cells (Fig. 1) [46,47]. Additionally, endothelial-cell-derived IL-15 induces transendothelial migration of T-cells and increases T-cell motility [48]. Taking this into consideration, it can be concluded that IL-15 influences endothelial cell biology, promoting angiogenesis and extravasation of cells. IL-15 also decreases apoptosis in many cell types, such as epithelial cells [49,50], fibroblasts [50] and neurons [51] (Fig. 1). In some cases, such as in keratinocytes, it also facilitates proliferation [50]. Overall, IL-15 is an antiapoptotic cytokine with the exception (described previously) of white adipose tissue, where the cytokine exhibits a very clear proapoptotic behaviour [38].

IL-15: main plasma changes

Chronic administration of IL-15 to experimental animals results in decreased triacylglycerol, insulin and leptin concentrations. The decrease in triacylglycerols observed in the VLDL fraction reinforces the reported action of the cytokine on liver lipogenesis [43], albeit contrasting with the effects on white adipose tissue LPL [31]. The decreased leptin levels [31], a peptide that influences food intake and adipose tissue mass, support the effects of IL-15 on adipose tissue mass (see IL-15 and white adipose tissue: regulation of fat-free mass section). It has also been speculated that IL-15 could be used in the treatment of diabetes, because it facilitates the uptake of glucose by skeletal muscle [19]. The fact that chronic IL-15 administration decreases insulin [29] without influencing glycaemia reinforces this hypothesis. In line with this observation is the work of Kuczynski *et al*. demonstrating the elevation of IL-15 in type I diabetes mellitus patients, implying that the cytokine could have a counteracting role to insulin during type I diabetes [52].

Therapeutic implications: a role for IL-15 in reciprocal regulation of the fat-muscle axis

Taking into account all of the above-mentioned cellular and metabolic effects of IL-15, it can be concluded that the cytokine could have therapeutic potential in at least three types of conditions: immunological problems, obesity and wasting. Indeed, IL-15 facilitates NK-cell proliferation and, therefore, it could be used to potentiate increased immune responses. In other cases, where exacerbated immune response occurs, such as psoriasis, blocking IL-15 may be a valid therapeutic option. Indeed, in psoriasis, keratinocyte proliferation is involved in skin plaque formation and, as has been suggested, IL-15 facilitates the proliferation of such cells [50], suggesting a clear role for the cytokine in the pathogenesis of psoriasis [49]. In obesity, the therapeutic application of the cytokine seems obvious because of the antiadipogenic effects of IL-15, mainly based on the inhibition of lipogenesis [31] and the induction of apoptosis [38] of white adipose cells. The effects of IL-15 in facilitating glucose uptake by insulin sensitive tissues (mainly skeletal muscle) [19] is important not only from the point of view of obesity, but also from the associated morbidities, such as type II diabetes. We have previously hypothesised that there is a reciprocal control between adipose and skeletal muscle size [53]. We propose that IL-15 is released from skeletal muscle with the aim of controlling fat deposition and, thus, white adipose tissue growth and mass. A muscle-derived cytokine would, therefore, not only contribute to skeletal muscle growth, but also participate, to some extent, in the regulation of body fat synthesis and deposition. We have already seen and commented on the fact that a similar situation is observed in adipose tissue [53], where several molecules are produced and released and have a direct action in skeletal muscle [53]. An example found in adipose tissue is leptin, which is capable of decreasing protein synthesis in skeletal muscle [54], acting in an opposite fashion to IL-15 [31]. In conclusion, a reciprocal regulation between adipose tissue and skeletal muscle may exist and may participate in the control of body weight, by regulating the normal (balanced) deposition of fat and protein in adipose and skeletal muscle tissue, respectively.

Finally, IL-15 could be used as a therapeutic approach to the treatment of wasting diseases. Indeed, animal studies clearly show the anabolic behaviour of the cytokine on skeletal muscle, based mainly on the inhibition of protein degradation, the main event activated in skeletal muscle during wasting conditions [20,22].

In conclusion, research efforts should, in the near future, concentrate on further pre-clinical investigations that may serve to design and perform clinical trials on the effects of the cytokine on the above-referred pathologies.

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