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REVIEW

IL-33 in obesity: where do we go from here?

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Abstract

IL-33 is a cytokine that belongs to the IL-1 family and is classically associated with type 2-like immune responses. In the adipose tissue, IL-33 is related to the beiging of adipocytes and to the maintenance of adipose tissue-resident immune cells, such as innate lymphoid cells 2, alternatively activated macrophages and regulatory T cells, which contribute to the maintenance of adipose tissue homeostasis. In the obese adipose tissue, the number of these cells is diminished, unlike the expression of IL-33, which is up-regulated. However, despite its increased expression, IL-33 is not able to maintain the homeostasis of the obese adipose tissue. IL-33 treatment, on the other hand, highly improves obesity-related inflammatory and metabolic alterations. The evidence that exogenous IL-33, but not adipose tissue-driven IL-33, regulates the inflammatory process in obesity leaves a gap in the understanding of IL-33 biology. Thus, in this review we discuss the potential mechanisms associated with the impaired action of IL-33 in obesity.

Keywords Inflammation · Type 2 innate lymphocyte · Beige adipocyte · ST2; metabolism

Introduction

IL-33, formerly named as nuclear factor from high endothelial venules (NF-HEV), is a cytokine that belongs to the IL-1 family, signals through the Suppression of Tumorigenicity 2 (ST2) receptor and induces both type 1 and type 2 immune responses [1]. This cytokine has gained attention in the past years for being related to a variety of diseases, including myocardial infarction, asthma, rheumatoid arthritis and obesity [2–5]. In obesity, a switch from a type-2 to a type-1 immune profile is well observed in the adipose tissue [6–8]. Because IL-33 can elicit a type-2 immune response, studies have shown that IL-33 administration to obese mice restores the immunological and metabolic profiles of adipose tissue [8–10], showing a protective effect of IL-33 in obesity. However, paradoxically, IL-33 expression is upregulated in obesity [11]. Thus, although the role of IL-33 in adipose tissue homeostasis has been fairly described, less is known about the changes that obesity causes in the biology of this cytokine, specifically in the adipose tissue. In this review, we discuss how obesity can impair the biology of IL-33.

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IL-33 expression pattern and function

IL-33 expression has been reported in many cell types, including resting dendritic cells, activated macrophages, fibroblastic reticular cells from lymphoid tissues and epithelial cells [1, 12–15]. Among these, epithelial cells constitute the major source of IL-33. Although they constitutively express IL-33, many inflammatory conditions, such as colitis, Crohn's disease and rheumatoid arthritis are associated with increased IL-33 expression by epithelial cells [13–15]. Moreover, IL-33 is also expressed by murine cardiac fibroblasts in response to mechanical stress and by endothelial cells in atherosclerotic sites [16, 17]. Thus, although being constitutively expressed by different cell types, IL-33 expression is upregulated in response to inflammatory stimuli.

It is proposed that the main biological effect of IL-33 is the induction of type-2 inflammatory responses, although its involvement in type-1 cytokines production has also been demonstrated [18–20]. Exogenous administration of IL-33 to mice causes blood eosinophilia and lymphocytosis, as well as splenomegaly, due to increased number of eosinophils, mononuclear and plasma cells in the spleen [1]. They present elevated IgE and IgA serum levels, as well as high mRNA expression of IL-4, IL-5 and IL-13 in the thymus, spleen, liver and small intestine [1, 21]. IL-33-injected mice also show increased mucus production and epithelium remodeling in the digestive and respiratory tracts [1].

A variety of cells is activated by IL-33. In vitro, IL-33 acts as a chemoattractant for T helper 2 (Th2) lymphocytes and induces the production of IL-5 and IL-13 by these cells [1, 22]. IL-33 is also a strong inducer of regulatory T cell (Treg) expansion, both in vitro and in vivo, and it upregulates the expression of type 2 cytokines by these cells [23–25].

Macrophages produce IL-5 and IL-13 in response to in vitro treatment with IL-33, whereas basophils respond to this stimulus by producing IL-4 [26, 27]. Mast cells can produce IL-6 and IL-13 in response to IL-33, and this cytokine has also been linked to survival and adhesion of mast cells to fibronectin [28, 29]. IL-33 also promotes survival of eosinophils, induces the production of IL-4 and IL-13 by these cells, and triggers the expression of a variety of genes, including retnla, epx, CXCL10, and CXCL17 [30, 31].

Another target of IL-33 is type-2 innate lymphoid cells (ILC2). Adipose tissue-associated c-Kit + Sca-1 + lymphoid cells, for example, produce large amounts of IL-13 in response to IL-33, which leads to goblet cell hyperplasia [32], and IL-33 is also responsible for ILC2 expansion in vivo [33, 34]. These effects of IL-33 in immune cells are consistent with its involvement in allergic and anthelmintic responses [32, 34, 35].

IL-33 effects are not restricted to the activation of cells involved in type-2 immunity. It has been demonstrated, for example, that IL-33 is necessary for proper CD8 and NK cells' effector function, including IFN-γ secretion in viral infections [36, 37]. IL-33 also stimulates the production of IFN-γ by iNKT and T cells [18, 38]. The activation of neutrophils can be mediated by IL-33 as well. In vitro, pre-treatment of neutrophils with IL-33 enhances their phagocytic activity, and neutrophils harvested from IL-33 treated mice also display improved phagocytosis [39, 40]. IL-33-primed neutrophils display increased fungal killing activity, which is associated with higher levels of reactive oxygen species production [39]. IL-33 also enhances neutrophil chemotactic activity [41].

Recent data suggest that IL-33 function goes far beyond activation of cells, as demonstrated by the role of oligodendrocyte-derived IL-33 as a mediator of neuropathic pain [42]. Therefore, IL-33 is a pleiotropic cytokine that induces both type-1 and type-2 responses and is expressed mainly by epithelial cells in a steady state or in response to inflammatory stimuli. It has been suggested that constitutive versus inducible expression of ST2 could explain how IL-33 plays crucial roles in both type-1 and type-2 responses [43]. Moreover, the balance between type-1 and type-2 effects of IL-33 can determine whether it exerts protective or pathological roles in the context of diseases [41, 44]. Thus, it is not surprising that IL-33 is implicated not only in allergic, but also infectious, metabolic and inflammatory diseases (such as atherosclerosis and type 1 diabetes), as well as in different contexts of pain [36, 42, 44–47].

The effects of IL-33 are mediated through the IL-33 receptor (IL-33R) complex, composed by the ST2 receptor and the Interleukin 1 Receptor Accessory Protein (IL-1RAcP) (Fig. 1). Biotinylated IL-33 binds to mast cells, which naturally express ST2, and this cytokine also prevents the binding of anti-ST2 antibodies to mast cells [1]. IL-1RAcP$^{-/-}$ mice do not respond to exogenous IL-33 administration, and IL-33 fails to induce IL-5/IL-13 and IL-6 expression by Th2 lymphocytes and mast cells harvested from IL-1RAcP$^{-/-}$mice [21]. The binding of IL-33 to its receptor leads to the recruitment of MyD88, IRAK, IRAK4, and TRAF6 to the ST2 receptor, resulting in the phosphorylation of IkBa, NF-kB, and the MAP kinases Erk1/2, p38, and JNK. The requirement of ST2 activation for these events is evidenced by the fact that IL-33-mediated phosphorylation of NF-kB, Erk1/2 and p38 is inhibited by an anti-ST2 antibody [1].

Besides its receptor-dependent effects, it has been proposed that IL-33, similarly to IL-1α, also acts as a nuclear factor. In fact, IL-33 was first described as a nuclear factor expressed in human high endothelial venules [12]. The same group also showed multiple nuclear heterochromatin domains of HEV enriched with IL-33 and proposed that,

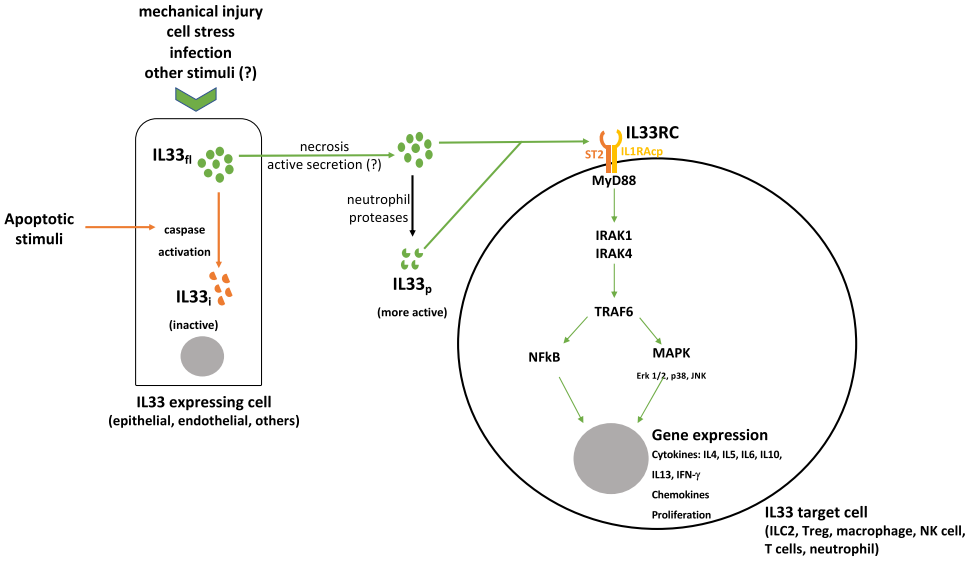

Fig. 1 IL-33 processing and signaling. *IL33fl* full length IL-33, *IL33i* inactive fragments of IL-33, *IL33p* processed IL-33, *IL33RC* IL-33 receptor complex, *ST2* suppression of tumorigenicity 2, *IL1RAcp* interleukin 1 receptor accessory protein, *ROS* reactive oxygen species

as a nuclear factor, IL-33 would acts as a transcriptional repressor. As proposed by Ali et al. [48], IL-33 acts as negative modulator of NF-kB. IL-33 binds to the p65 and p50 NF-kB subunits, both in cell nucleus and cytoplasm, and this interaction interferes with the p65-DNA binding capacity and transcription function. More recently, it was shown that fibroblast-like synoviocytes treated with IL-33 siRNA have reduced IkB expression in response to IL-1β and TNF-α stimulation, and that IL-33 silencing also increased NF-kB activation by IL-1b and TNF-α [49]. However, Gautier et al. [50], using a global proteomic approach, showed that endogenous IL-33 knockdown had no effect on endothelial cell proteome, nor on the regulation of NF-kB protein expression. This can be explained by the findings of Ali et al. [48], who showed that IL-33 interaction with NF-kB delays but does not inhibit the expression of NF-kB-regulated genes. In this way, IL-33 shares with IL-1α and high-mobility group box 1 (HMGB1) protein a dual function, as a cytokine and a nuclear factor, although its biology as a nuclear factor remains to be elucidated.

IL-33 processing and secretion

The cytokines of the IL-1 family, such as IL-1β and IL-18, are produced as pro-peptides that must be processed by proteases, like caspase-1, to achieve biological activity and secretion. The same was proposed for IL-33 by Schmitz et al. [1], who demonstrated that an in vitro translated form of IL-33 was cleaved by recombinant caspase-1, generating a fragment of 18 kDa. A later study confirmed the occurrence of this reaction in vitro, however, the IL-33 fragments generated by caspase-1 cleavage ($IL\text{-}33_{1-178}$ and $IL\text{-}33_{179-270}$) failed to activate ST2-dependent signaling and IL-6 secretion by the mast cell line MC/9 [51]. In disagreement with the evidences that IL-33 is a substrate for caspase-1, other three studies could not find in vitro cleavage of human or mouse IL-33 by caspase-1 [52–54]. Moreover, two of these studies assessed whether this reaction happens at a cellular level by treating THP-1 cells with LPS, a trigger for caspase-1 activation, but no evidence of IL-33 processing by caspase-1 was found [53, 54]. Ohno et al. [55] have also demonstrated that, besides caspase-1, IL-33 secretion by macrophages is also independent of caspase-8 and calpain activity. More recently, it has been shown that lack of caspase-1 results in an increase of full length IL-33 detected in the lung of mice with dust mite-induced allergic lung inflammation [56], suggesting an in vivo role of caspase-1 in the processing of IL-33. However, the $Casp1^{-/-}$ model used in the study was also deficient for caspase-11, not allowing the conclusion of whether the increased secretion of IL-33 in its full-length form was a result of caspase-1 or caspase-11 absence. As observed by Talabot-Ayer et al. [54], other cellular proteases may be involved in the processing of IL-33, and the findings of Madouri et al. [56] may indicate that caspase-11 is one of them. Thus, different from other cytokines of the IL-1 family, the role of caspase-1 in the biology of IL-33 is still unclear.

These findings led to the hypothesis that IL-33, as well as IL-1α, does not need processing to gain biological activity. In fact, full length IL-33 efficiently binds to and signals through the ST2 receptor [51–53]. Moreover, the intact version of this cytokine is able to induce expression of IL-6 by mast cells [51, 54]. Because IL-33 is active as a full-length molecule, does not require caspase-1 cleavage for its activation and secretion, and has a nuclear localization, it has been proposed that IL-33 acts mainly as an alarmin released from necrotic and/or damaged cells. In this aspect, some studies

could not detect IL-33 in the medium of intact cells upon stimulation with LPS and PMA, despite increased cellular IL-33 expression [51, 53]. Release of IL-33 was observed only after necrosis or mechanical damage of THP-1 and endothelial cells. In addition, the idea that this cytokine functions as an alarmin is reinforced by the fact that IL-33 is constitutively expressed in the epithelium of barrier tissues and induced upon inflammation [14, 15]. Together, these findings suggest that IL-33 acts through a "necrocrine" pathway, being specifically released upon necrotic cell death that follows tissue trauma or infection [57]. However, this passive pathway for IL-33 release is not sufficient to explain the high concentration of IL-33 in the serum of patients who survived sepsis [48], or its presence in lung supernatant collected from mice with lung inflammation [56, 58]. Thereafter, up to now, many aspects of IL-33 processing and secretion remain enigmatic.

Although it is now accepted that IL-33 is biologically active in its full-length form, its biology can be regulated by proteases other than pro-inflammatory caspases. IL-33 is cleaved, in vitro, by the caspases-3 and 7. Induction of cellular apoptosis also leads to IL-33 cleavage [51–53], a process that is abrogated upon mutation at the caspase-3 cleavage site [52, 53] and in the presence of caspase-3 inhibitors [52]. IL-33 processing by caspases-3 and 7 abrogates its biological function, once IL-33 fragments obtained after cleavage fails to activate NF-kB [52, 53]. It is proposed that IL-33 inactivation by pro-apoptotic caspases is important to the abrogation of its pro-inflammatory effects during apoptosis [59]. In contrast, IL-33 fragments generated by the action of neutrophil serine proteases, such as elastase and cathepsin G, have approximately 10-fold higher biological activity than the full-length IL-33 [58]. This interaction between neutrophil proteases and IL-33 seems to happen in vivo, as observed by the presence of cleaved IL-33 in the bronchoalveolar lavage fluid of mice that had lung damage accompanied by neutrophil infiltration [58]. Hence, these data show that, although IL-33 is active as a full-length molecule, the fragments generated by different proteases can have either enhanced or impaired function. The determination of the biological significance of these events is necessary for a complete understanding of the IL-33 biology.

IL-33 role in adipose tissue homeostasis

In recent years, the role of IL-33 in the homeostasis of visceral adipose tissue has emerged. The presence of IL-33 in human adipose tissue was first described by Wood et al. [60]. They reported the expression of both IL-33 mRNA and protein, as well as ST2 and IL1RAcP mRNA, in the omental white adipose tissue of obese individuals. The authors also showed constitutive expression of IL-33 by cultured pre- and mature adipocytes, as well as increased IL-33 expression by these cells in response to TNF-α stimulation. IL-33, ST2 and IL1RAcP expression in human adipose tissue was later confirmed by Zeyda et al. [11], who showed that endothelial cells were the main source of IL-33 in the adipose tissue. A role of IL-33 in the cross-talking between adipocytes and adipose tissue-resident immune cells was then proposed.

The lean visceral adipose tissue recruits and sustains distinct types of immune cells, such as type-2 innate lymphoid cells (ILC2), eosinophils, alternatively activated macrophages (AAM) and Tregs. These cells are responsible for the maintenance of a type 2-polarized, anti-inflammatory environment and for the control of local metabolism, and a role for IL-33 in this process has been proposed (Fig. 2). Treating mice with IL-33 increases the number

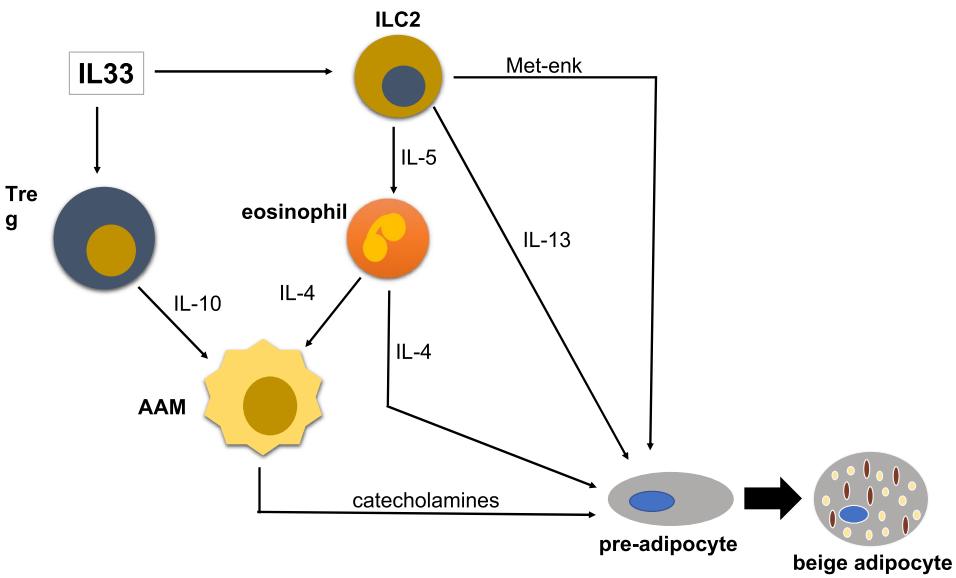

Fig. 2 – IL-33 role on adipose tissue metabolic homeostasis. *Treg* regulatory T cell, *ILC2* type-2 innate lymphoid cells, *AAM* alternative activated macrophage, *Met-enk* Met-enkephalin

and activation of adipose tissue-ILC2 [61, 62], but the deletion of IL-33 diminishes the number and frequency of these cells, as well as their expression of IL-5 and IL-13 [9]. IL-33-treated mice also accumulate eosinophils in the adipose tissue [61, 62], but this process is abrogated in the absence of ILC2 or IL-5 [61]. Moreover, mice treated with IL-33 have an increased proportion of adipose tissue AAM, but IL-33 fails to cause this effect in the absence of IL-C2 [61], showing that IL-33-driven accumulation of eosinophils and macrophages in the adipose tissue is dependent on ILC2. The maintenance of visceral adipose tissue (VAT) Treg cells, which present high expression of ST2 [24], is also dependent on IL-33. IL33$^{-/-}$ or ST2$^{-/-}$ mice have a notable decrease in the number of VAT Tregs [23, 24]. Moreover, IL-33 is able to expand the VAT Tregs in vivo and in vitro [23, 24], without the need for TCR (T cell receptor) engagement [24]. Thus, IL-33 is a potent inducer of Treg expansion and an important factor for the accumulation of VAT Tregs.

In addition to the effects on VAT-resident immune cells, IL-33 also contributes to the control of adipose tissue metabolism. Treating lean mice with IL-33 causes an increase in caloric expenditure, without affecting physical activity and food intake [9]. On the other hand, mice lacking either IL-33 or ST2 and receiving a normal diet gain more weight and develop greater adiposity than wild-type mice [8, 9]. In obesity, IL-33 treatment causes a reduction in both fat mass and body weight [8, 9, 23], which can be a result of an imbalance between energy storage and expenditure. IL-33 treatment leads to a reduction in adipocyte mean size [8, 23], and as reported by Miller et al. [8], IL-33 downregulates the expression of genes associated with adipogenesis and inhibits the accumulation of fat during in vitro-adipocyte differentiation. Besides decreasing adipocyte-energy storage, IL-33 increases energy expenditure through the induction of beige adipocytes, cells that efficiently produce heat through a UCP-1 dependent-thermogenic process [62–64]. IL-33 administration to lean mice increases the expression of UCP-1 in white adipose tissue, as well as the number of UCP-1 + beige adipocytes [9, 62]. On the other hand, IL33$^{-/-}$ mice have few beige adipocytes and reduced UCP-1 expression in white adipose tissue [9]. More recently, it was demonstrated that the IL33/ST2 pathway is necessary for beige adipocyte-UCP-1 expression at the time of weaning and upon cold exposure, as IL-33$^{-/-}$ and ST2$^{-/-}$ mice fail to upregulate white adipose tissue-UCP-1 expression in both situations [65]. The ability of IL-33 to increase energy expenditure and decrease fat accumulation demonstrate how IL-33 influences adipose tissue metabolism to favor the control of body weight.

The effects of IL-33 on beiging of adipose tissue seems to be dependent on ILC2. The commitment of pre-adipocytes to a beige phenotype can be induced by IL-13 and IL-4 signaling via IL4-Ra receptor [62], two cytokines whose productions are induced by the activation of the IL-33/ILC2 axis. Beiging of adipocytes can also be accomplished by Met-enkephalin, a mediator produced by IL-33-activated ILC2 that increases adipose tissue-UCP1 expression and oxygen consumption [9]. However, in the absence of ILC2, IL-33 fails to induce the production of UCP-1, as well as the expression of the beige adipocyte markers TMEM26 and CD27 [9, 62], which demonstrates that ILC2 are the mediators of IL-33 adipose tissue beiging effects. IL-33, via both ILC2 and Treg, is also necessary to maintain AAM in the adipose tissue, which contributes to adipocyte beiging through catecholamines secretion [66, 67]. These data indicate that IL-33 controls adipose tissue homeostasis via the activity of ILC2.

IL-33 in obesity: where do we go from here?

Obesity causes a disturbance in body homeostasis, leading to metabolic and inflammatory alterations. The inflammatory changes are well observed in the adipose tissue, where there is a decrease in the number of resident-ILC2, eosinophils, AAMs and Tregs [6, 9, 10, 68]. On the other hand, there is an increase in adipose tissue-proinflammatory cells, such as M1 macrophages, Th1 lymphocytes and neutrophils [7, 9, 69]. Moreover, an unbalance between type 1 (IL-1, IL-6 and TNF-α) and type 2 (IL-10, IL-4) cytokines is seen in obesity [6, 10, 70]. Thus, anti-inflammatory components are overshadowed by pro-inflammatory factors, which establishes a type 1 inflammatory state that somehow contributes to the metabolic changes associated with obesity, exemplified by impaired glucose tolerance and insulin resistance [8–10].

In this context, IL-33 can modify obesity outcomes. As shown by Miller et al. [8], spontaneously obese mice (*ob*/*ob*) injected with recombinant IL-33 present reduced visceral adipose tissue and mean adipocyte size, despite no effect on body weight and food intake. In addition, IL-33 treatment increased the production of IL-5, IL-6 and IL-10 with no effect on the levels of TNF-α and MCP-1. The profile of immune cells in the adipose tissue was also modified, evidenced by higher number of AAMs and IL-5 producing-Th2 cells. Similar findings were observed in models of high-fat diet-induced obesity [9]. Moreover IL-33 treatment restores the proportion of VAT Treg cells and reduces the number of infiltrating macrophages in the adipose tissue of obese mice, which is accompanied by lower expression of TNF-α mRNA and higher insulin sensitivity [10, 23]. These findings show that IL-33 induces protective effects in obesity.

In humans, a protective role for IL-33 in obesity has also been proposed. Hasan et al. [2] investigated the association between serum IL-33 levels and body mass index (BMI)/metabolic profile of lean and obese individuals. They showed that overweight subjects have reduced serum levels

of IL-33 compared to lean individuals, and a negative correlation of IL-33 with BMI was also observed. Thus, IL-33 works toward the resolution of inflammation and metabolic alterations associated with obesity, showing that this cytokine is important to the homeostasis of the adipose tissue not only in normal conditions, but also in pathological settings such as obesity.

Because IL-33 influences adipose tissue metabolism and sustains a local type-2 polarized environment, it would be reasonable to assume that IL-33 expression and/or function are dysregulated in obesity. As demonstrated by Zeyda et al. [11], omental adipose tissue of obese subjects has greater IL-33 mRNA and protein expression compared with lean to overweight subjects. This observation was also replicable in mice [11, 23], although Ding et al. [71] reported a reduction on IL-33 expression in the subcutaneous adipose tissue of mice treated with a high fat diet. When it comes to the IL-33 receptor, ST2 gene expression is also upregulated in the adipose tissue of obese humans and mice [11]. Thus, in the pro-inflammatory context of obesity, the increased IL-33 expression is paradoxical. In this notion, why does IL-33 fail to control inflammation and metabolism in obese adipose tissue, despite its high expression?

The literature already has some answers to this question and many other clues about the dysfunctional response of IL-33 in obesity, offering a vast field for future investigations (Fig. 3). The expression of the soluble form of ST2 (sST2) is increased in obese subjects [11], and sST2 correlates with insulin resistance, the main metabolic complication of obesity that leads to diabetes [72]. In this way, the protective effects of IL-33 in obesity can be abrogated by sST2, despite IL-33-increased expression.

It can also be hypothesized that IL-33 is not fully active in obesity. Because the expression and activity of caspase 3 is increased in the adipose tissue of obese mice [73], it is reasonable to propose that IL-33 is being inactivated by caspase-3 in obesity, which unable IL-33 to maintain a type 2 immunological profile in the obese adipose tissue, despite its high expression. Although Zeyda et al. [11] have reported increased levels of IL-33 protein in the adipose tissue of obese mice and humans by ELISA and immunoblotting techniques, it may be argued whether the anti-IL-33 antibodies

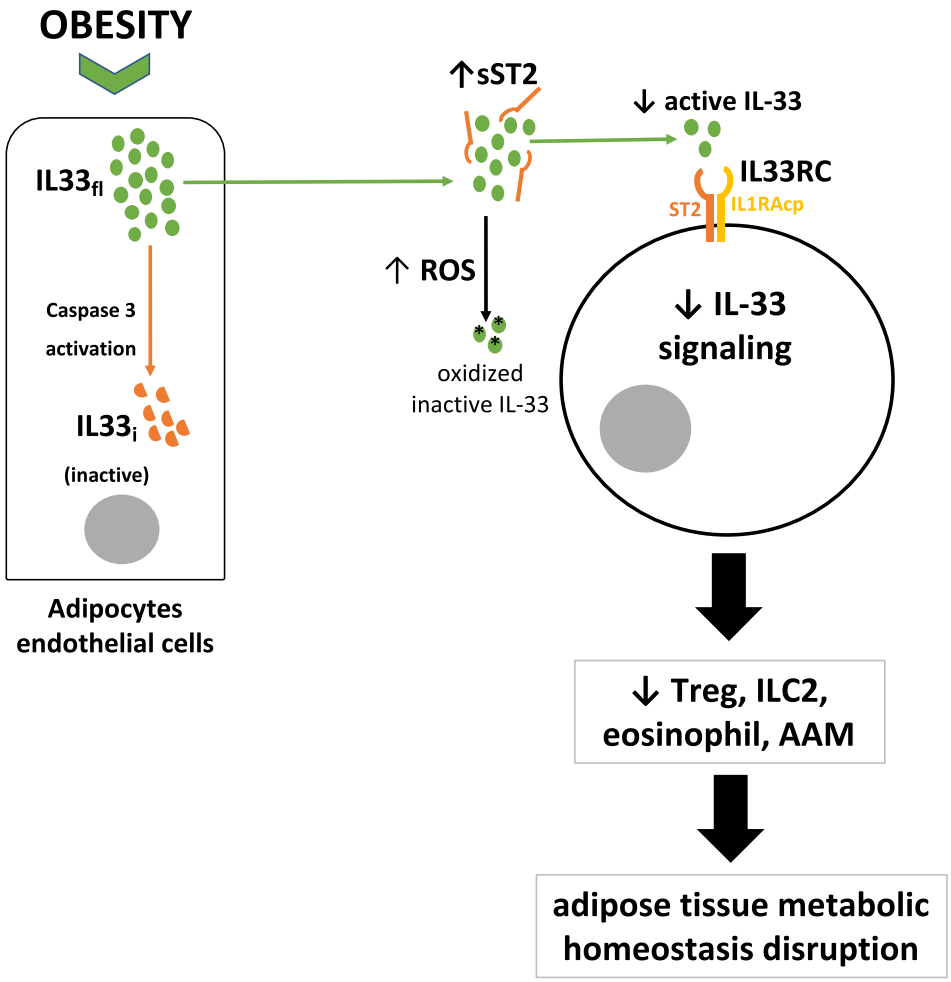

Fig. 3 Dysfunctional IL-33 signaling in obesity. Reduced IL-33 function in obesity may be a consequence of increased caspase 3 activity, oxidative stress, neutralization by sST2, amongst others. *ROS* reactive oxygen species, *ST2* suppression of tumorigenicity 2 receptor, *sST2* soluble form of ST2, *IL-33i* inactive fragments of IL-33. *fl-IL-33* full length IL-33, *Treg* regulatory T cell, *ILC2* type-2 innate lymphoid cells, *AAM* alternative activated macrophage

employed in the study can distinguish between full-length/active and processed/inactive IL-33.

Not only caspase 3, but also caspase-1 and the NLRP3 inflammasome (responsible for caspase 1 activation) are upregulated in obesity [70, 74]. Caspase 1 plays a role in the maturation of the IFN-γ-inducing factor (IGIF) and directs its expression by immune cells [75]. IFN-γ is highly expressed by Th1 lymphocytes in the adipose tissue of obese mice [7], and this cytokine counteracts the positive effects of IL-33 on adipose tissue-ILC2 and Treg cells [76]. Caspase-1/NLRP3 inflammasome also activates IL-1β secretion, another cytokine that contributes to the metabolic disturbances of obesity [70]. IL-1β enhances the production of sST2 [77, 78] and so increased secretion of IL-1β can disrupt IL-33 signaling via its neutralization by sST2. Thus, the contribution of caspase 1 to the expression of IFN- γ and IL-1β might be another mechanism by which this protease limits IL-33 function in the adipose tissue of obese mice.

Other factors could also impair IL-33 signaling in obesity. This disease is related to increased oxidative stress in the adipose tissue, evidenced by upregulation of reactive oxygen species and downregulation of antioxidant enzymes [79]. Cohen et al. [80] reported that oxidation of IL-33 at the cysteine sites leads to the formation of disulfide bridges that alter the ST2 binding site, preventing IL-33 from signaling through its receptor. In this notion, the adipose tissue microenvironment may facilitate the occurrence of IL-33 oxidation, thus consisting of another mechanism for IL-33 inactivation in the adipose tissue.

In face of these hypotheses, how could administration of IL-33 ameliorate obesity when exogenous IL-33 is also exposed to the same local environment that possibly impairs endogenous IL-33 function? In obesity, neutrophils infiltrate the adipose tissue and secrete elastase, an enzyme that plays a key role in the establishment of local inflammation [69]. As demonstrated by Lefrançais et al. [58], neutrophil elastase-processed IL-33 is biologically more active. Hence, although elastase is detrimental in the context of obesity, this enzyme might contribute to an improvement in the activity of administrated IL-33, overcoming the effects of obesity on IL-33 biology. A more active form of IL-33, due to neutrophil elastase activity in obesity, could partially explain why IL-33 treatment is so efficient in regulating the obesity-related adipose tissue inflammation.

Conclusion

Because IL-33 has a protective effect against obesity, mediated by its role on type 2 immune cells, it would be reasonable to propose that its expression is reduced in obesity. However, paradoxically, IL-33 expression is increased in obesity, which indicates that its biology is impaired in this condition. Mechanisms involved in the modification of IL-33 action in obesity are summarized in Fig. 3, and they include: IL-33 neutralization by the soluble form of its receptor; IL-33 cleavage and inactivation by caspases up regulated in obesity; counteraction of IL-33 effects on Treg and ILC2 by IFN-γ; and IL-33 inactivation by obesity-induced oxidative stress. Despite this adverse environment, exogenous IL-33 administration partially reverses the inflammatory and metabolic derangements of obesity. The effects of exogenous IL-33 in the adipose tissue may be improved by neutrophil elastase, which is highly expressed in the obese adipose tissue. Given the increased expression of IL-33 in obesity, modifications in this unfavorable environment, even if little, may play an important role in the restoration of adipose tissue homeostasis in obesity.

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