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Resistin, a Multipotential Therapeutic Target

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Abstract: Being overweight and obese are risk factors that have increased during the COVID-19 pandemic; these factors increase the white adipose tissue (WAT) that increases the release of adipokines (adiponectin, leptin, and resistin). So, obesity provokes the expansion of adipose tissue; it induces changes in their macrophages of pro-inflammatory cytokines (M2 to M1). These changes increase the resistin levels with effects on the metabolism, inflammation process, glucose homeostasis, and insulin resistance, promote cell proliferation and migration, and even serve as a biomarker for tumorigenesis. Therefore, resistin is proposed as a multipotential therapeutic target to treat different diseases, between chronic-degenerative and some types of cancer, because resistin has characteristics that give it a high probability to be a therapeutic target to attend to and prevent various diseases. In different ways, developing new drugs by molecular docking to use molecules with pharmacological characteristics capable of interacting in the regions of resistin to hinder/block the interaction between resistin and their receptors (Δ-DCN, TLR4, and CAP-1) and by promoting health to reduce overweight and obesity, and this could generate lower plasma serum resistin values, so this review remarks the potential of resistin as multipotential therapeutic target.

Keywords: resistin; obesity; T2DM; pro-inflammatory cytokines; cancer.

1. Introduction

Overweight and obesity have increased in the last 2 years, increased by the COVID-19 pandemic [1-5], and the consequences of the relationship between stress with obesity increase the white adipose tissue (WAT) [6]. These risk factors are present in several acute and chronic degenerative diseases and cancer [7-12]. So, obesity provokes the expansion of adipose tissue; it induces changes in their macrophages (M2 to M1) by releasing chemokines that induce increased recruitment of M1 macrophages from the bloodstream [13,14]. The macrophages are an important part of the secretory function of adipose tissue and the main source of pro-inflammatory cytokines because they can promote gene expression alteration and insulin resistance in adipocytes [15].

In addition, an increase in WAT increases the secretion of adipokines (adiponectin, leptin, and resistin) [9-11,15,16]. The resistin has taken relevance due to its contribution to regulating the metabolism, inflammation process, glucose homeostasis, and insulin resistance, and promotes cell proliferation and migration y secreted predominantly by WAT and macrophages [7,11,17,18], besides the knowledge that the resistin could have elevated levels in certain inflammatory-based disease [9,14,19].

2. Resistin in Blood

Resistin is a cysteine-rich hormone secreted from macrophages and white adipocytes mainly; it is founded in different structural forms, mainly as trimers, hexamers, and even polymers in blood [20].

It has been reported that serum concentrations of resistin are between 15 to 29 ng/ml [7,21]. These resistin values have different ways to regulate their concentration (some of them due to hyperglycemia, dexamethasone, and thiazolidinedione). As I mentioned, resistin has different functions and suppresses glucose uptake and insulin sensitivity in mice. Various pro-inflammatory stimuli promote the expression and secretion of resistin from human macrophages [14], suggesting that resistin plays a crucial role in inflammation, but it is not clear its receptor or receptors exerts the functions of the resistin; one resistin receptor proposed is a variant of decurin (Δ-DCN), Δ-DCN was detectable mainly in WAT, lung and bone marrow, and the Δ-DCN receptor is increased by obesity (to regulate WAT expansion) [17,21]; another resistin receptor proposed is the Toll-Like Receptor 4 (TLR4), that actives its signaling pathways [22]; and other resistin receptor proposed is the Adenylyl cyclase associated protein 1 (CAP-1), that could induce NF-κB gene expression, mediated by PKA, resulting in the expression of pro-inflammatory cytokines [14]. Therefore, the structural characteristics and the high number of cysteines in the sequence of resistin allow it to interact with several types of receptors so that resistin can be a potential target. Regulate the resistin can cause a therapeutic effect in their functions at the endocrine level, with a probable multitherapeutic or preventive effect, in the control of blood glucose levels, lipid metabolism, regulation of pituitary somatotropin cells, and the hypothalamic center of satiety [20,23].

3. Resistin in Metabolism

Resistin in plasma serum may be increased by different conditions in the body that may affect metabolism, in which a relationship can be with obesity, increased adipose tissue, M1 macrophages, contributing to the generation of insulin resistance, hyperglycemia, type 2 diabetes mellitus, and even with cancer [8,19,21,24-27].

Modifying resistin concentrations *in vivo* assays has shown its importance in regulating glucose and insulin concentrations; resistin knockout mice exhibit low blood glucose levels after fasting due to reduced hepatic glucose production [18]. In another study, resistin overexpressing in rats infected by adenovirus encoding mouse resistin displayed glucose intolerance and hyperinsulinemia, so resistin is related to insulin resistance and patients with type 2 diabetes mellitus [21].

Resistin can be in different structural conformations due to mainly trimers and hexamers [21]. These resistin polymers show more effects on many metabolic products, such as pro-inflammatory cytokines [28,29], triglycerides, and LDL cholesterol [26], among others. As mentioned, the interaction of resistin with TLR4 could be a key hormone linking insulin resistance by obesity (more WAT) by its signaling pathways on pro-inflammatory cytokines and to generate insulin-resistance/diabetes [16,19,20,22,27].

4. Resistin and the Inflammatory Response

Assessing the effect of resistin on the inflammatory response depends on the receptor that could be regulating/activating. Currently, at least three proposed receptors that generate feedback (Δ-DCN, TLR4, and CAP-1). Of these, the Δ-DCN receptor is related to the increase

of WAT [17,21]. Therefore, expansion of adipose tissue leads to adipocyte hypertrophy and the release of adipokines that induce increased recruitment of M1 macrophages from the bloodstream; this effect in cellular composition surrounding WAT generates a shift in the balance of anti-inflammatory macrophages (M2 phenotype) to pro-inflammatory macrophages (M1 phenotype). This change increases cytokine production, promoting adipose tissue dysfunction and impairment of glucose tolerance [13,14]. Another receptor identified, probably with greater importance, is the TLR4 and its signaling pathways, and if the concentration of resistin increases due to the increase of WAT and macrophages; the interaction between resistin and TLR4 can contribute to generating insulin resistance [22,27], and the last receptor proposed is the Adenylyl cyclase associated protein 1 (CAP-1) in cultured monocytes [30]. That could have an intracellular interaction with resistin (internalization of resistin may occur through endocytotic processes). It could increase the pro-inflammatory cytokines [14,20,27,31]. These changes result in altered adipokine secretion, increased lipolysis, and excess circulating nonesterified fatty acids, which may eventually contribute to systemic insulin resistance [15,19,22] (Figure 1).

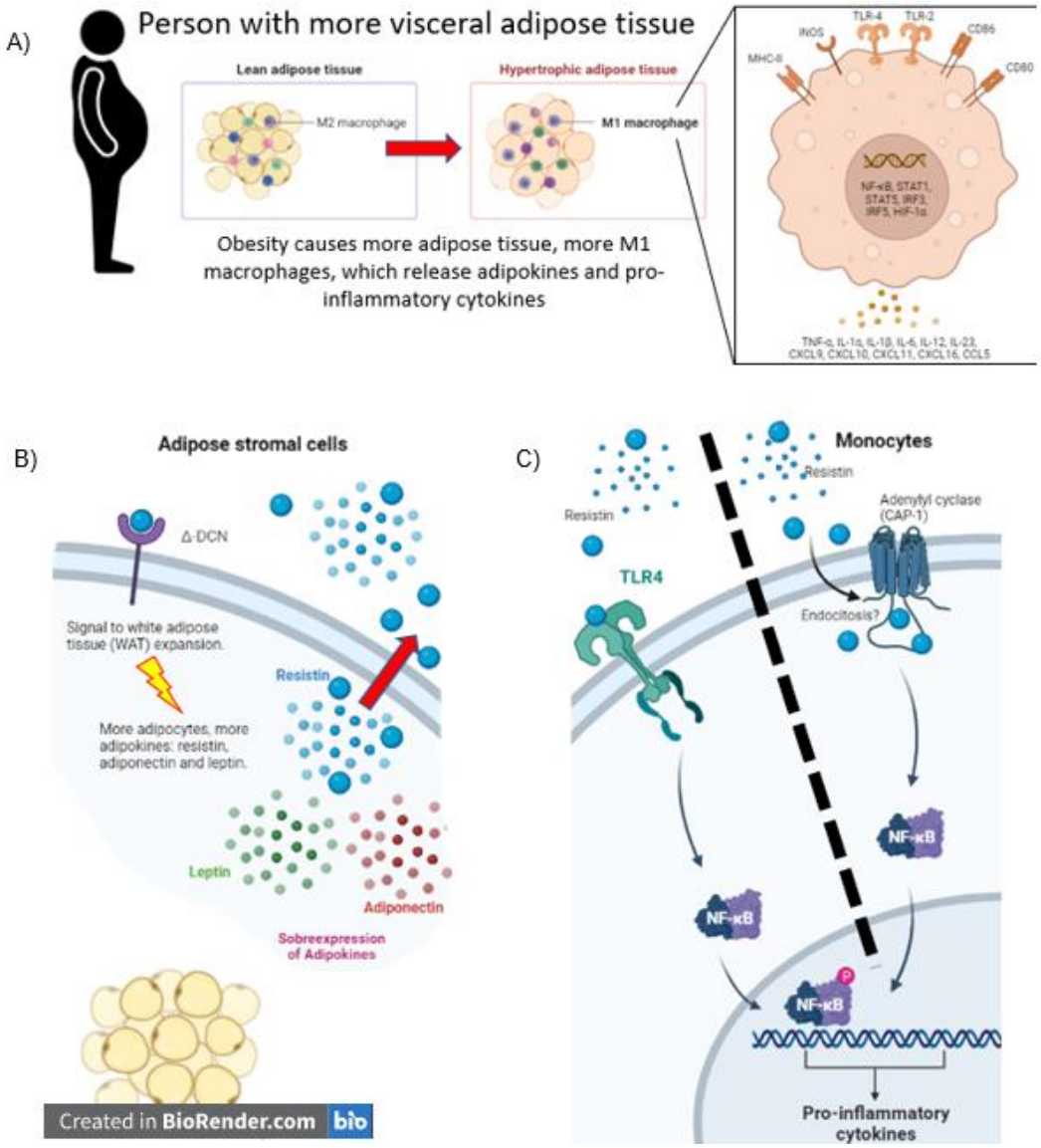

Figure 1. Different ways to increase resistin values. (**A**) obesity increases adipose tissue and recruitment M1 macrophage, releasing adipokines and pro-inflammatory cytokinesș (**B**) DCN receptor in adipose stromal cells that stimulate the WAT expansion and increase the secretion of adipokinesș (**C**) Release of pro-inflammatory cytokines by TLR4 and CAP-1 receptor in monocytes.

Also, there are studies that identify a causal link between cytokines and chronic fatigue syndrome [32], where the previous interactions between resistin and their probable receptors could release these cytokines and add this condition to affect physical activity and mental health.

On the other hand, it is necessary to consider another resistin effect, like an anti-inflammatory promoter by IL-10 expression [27]. The interaction of the N-terminal peptide of resistin with TLR4 [27] avoids the interaction of TLR4 with lipopolysaccharide (LPS), decreasing the STAT3 and TBK1-dependent mechanism. Therefore, resistin could modulate the TLR4 signaling pathway in two ways; to generate NFκB, which is pro-inflammatory, and TRIF/TBK1, which is anti-inflammatory and promotes IL-10 expression [27,33].

5. Resistin in Cancer

Another effect of resistin in the body that has become relevant is its role in the development and proliferation of different types of cancer [12] due to the consequences it could generate with the interactions with receptors mentioned (Δ-DCN, TLR4, and CAP-1). Also, resistin could be considered a biomarker for tumorigenesis [8]. For example, in breast cancer, the interaction between resistin and TLR4 is correlated with tumor stage, size, and lymph node metastasis [34], which promotes tumor progression via TLR4/NF-κB/STAT3 signaling, so high resistin expression in breast cancer tissues was positively associated with more malignant clinicopathological status and poor patient survival [34]. The higher serum resistin has also been reported to be associated with worse tumor stage and mortality, primarily in ERPR negative breast cancer [7]. These studies it is showing that resistin needs more attention when people are with obesity due to the increase in adipokines, such as leptin and resistin; these hormones have been linked to the risk of obesity-related cancers potentially through the inflammation pathways [7,11,12,35].

6. Resistin as a Potential Therapeutic Target

How could we regulate the resistin? It is necessary to check their conformation; resistin is mostly found in different conformations: trimer, hexamer, and oligomer, with a molecular weight of 660 kDa. The differences between the forms of resistin, as well as their biological activities, have not yet been clarified [15,20]. The disulfide and non-disulfide bonds have been important in the formation of higher-degree assembly states, these bonds have the ability to stabilize resistin structure, making it resistant in strongly denaturing environments [20], and the surface/structural characteristics and the high number of cysteines at one end of resistin [21], it could generate potential sites of interaction with molecules/compound with pharmacological characteristics, to search a new molecule by molecular docking that is interacting with resistin. These molecules most hinder/block the interaction between resistin and their receptors (Figure 2).

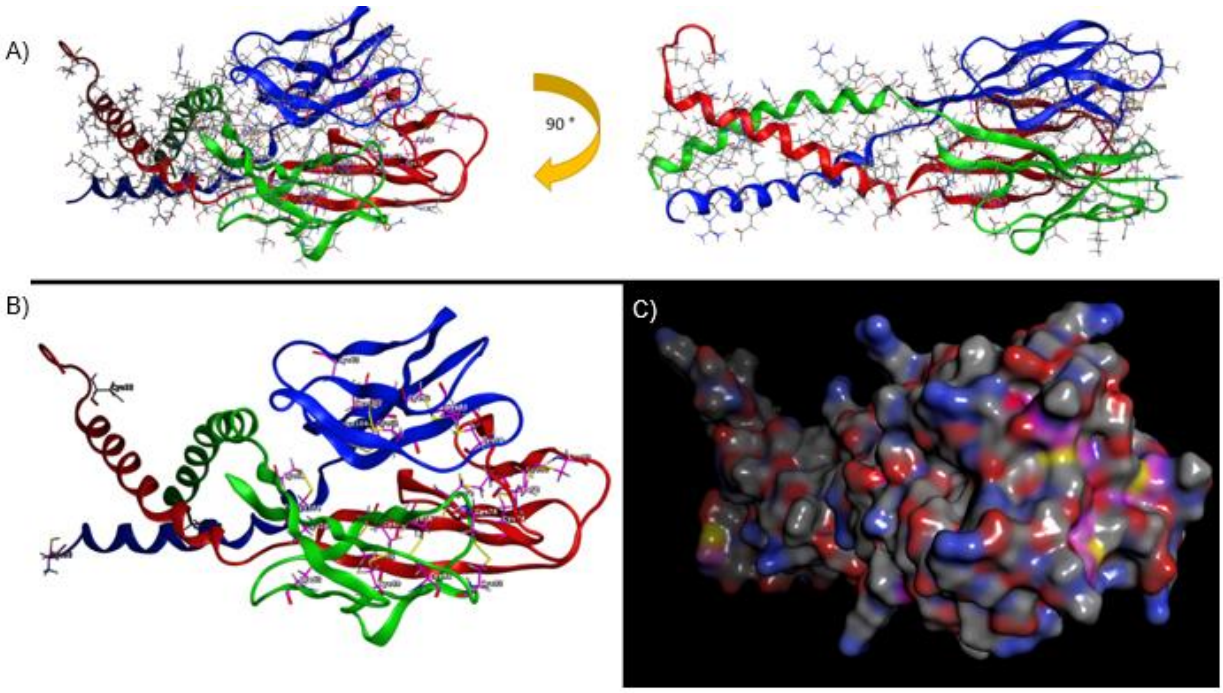

Figure 2. Resistin trimer modeled from PDB:1RGX. (**A**) Potential sites on the resistin trimer amino acids are showingș (**B**) Ribbon structure with many Cys amino acids (pink)ș (**C**) Resistin trimer surface with Cys amino acids, which show the potential site to interact with compounds or receptors.

7. Conclusions

Social problems and the ongoing pandemic have made eating problems more noticeable, so we might think that several diseases could be avoided simply by controlling and improving body weight. But it is clear that the problems of overweight and obesity will continue during this decade [3,13,16,36], which makes it necessary to increase efforts to reduce these risk factors that generate risk conditions, such as increased adipose tissue, increased release of adipokines, increased pro-inflammatory cytokines. All this contributes to generating insulin resistance and/or hyperglycemia, which even favors conditions for developing and proliferating some types of cancer [12].

In this review, resistin is proposed as a multipotential target to treat different diseases, between chronic-degenerative and some types of cancer; the effects of resistin in different diseases are still being evaluated due to resistin affecting several cell functions of different tissues [20]. Resistin participates in the inflammation process and oxidative stress, as well as develops insulin resistance leading to T2DM, and even could serve as a biomarker for tumorigenesis [8]; these findings provide insights into a novel therapeutic target that has a key role in various diseases, like cancer, insulin sensitivity, diabetes, thrombosis, among others [27,37].

Therefore, resistin has characteristics that give it a high probability of being a multipotential therapeutic target to attend to and prevent various diseases. One way to be able to regulate or decrease the functions of resistin would be to use molecules with pharmacological characteristics capable of interacting in the regions of resistin that are important to form resistin trimers, hexameres, or polymers to hinder/block the interaction between resistin monomers; on the other hand, these molecules could hinder/block the interaction between resistin (trimers, hexameres or polymers) and their receptors (Δ-DCN, TLR4, and CAP-1), this could decrease the functions of resistin despite the increased concentrations at blood level (Figure 3), where this new therapeutic strategy could to generate

the reduction of functions of resistin in plasma serum to regulate the role of resistin in some disease develop. The full role of resistin is still lacking. Other possible receptors and resistin conformations have greater activity in the organism, but more studies will be necessary to develop this therapeutic strategy.

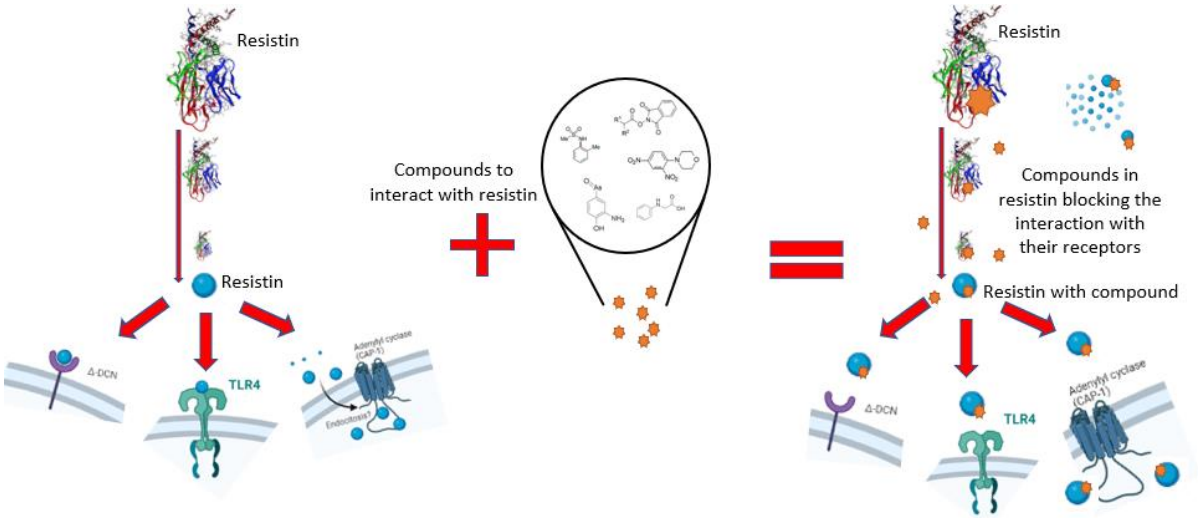

Figure 3. Blocking the interaction between resistin and their receptors (Δ-DCN, TLR4, and CAP-1), by compounds selective on resistin.

Finally, another way to regulate resistin is by promoting health to reduce overweight and obesity, which could generate lower plasma serum resistin values [7,9,21]. This way could impact public health and economic resources by reducing all the consequences of chronic degenerative diseases and some types of cancer-related to increased resistance due to obesity.

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Conflicts of Interest

The author declares no conflict of interest.

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