Resistin: A journey from metabolism to cancer

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ABSTRACT

Resistin, a small secretory molecule, has been implicated to play an important role in the development of insulin resistance under obese condition. For the past few decades, it has been linked to various cellular and metabolic functions. It has been associated with diseases like metabolic disorders, cardiovascular diseases and cancers. Numerous clinical studies have indicated an increased serum resistin level in pathological disorders which have been reported to increase mortality rate in comparison to low resistin expressing subjects. Various molecular studies suggest resistin plays a pivotal role in proliferation, metastasis, angiogenesis, inflammation as well as in regulating metabolism in cancer cells. Therefore, understanding the role of resistin and elucidating its associated molecular mechanism will give a better insight into the management of these disorders. In this article, we summarize the diverse roles of resistin in pathological disorders based on the available literature, clinicopathological data, and a compiled study from various databases. The article mainly provides comprehensive information of its role as a target in different treatment modalities in pre as well as post-clinical studies.

Introduction

Resistin, a pro-inflammatory cytokine was initially discovered by Dr. Mitchell Lazar Group as a link between two diseases-diabetes and obesity in 2001. It was found to mediate insulin resistance – hence the name ‘Resistin’ was coined. Resistin is primarily secreted from macrophages in humans whereas in rodents its main source is adipocytes. It is a ~12.5 KDa hormone, rich in cysteine residues and is encoded by the RETN gene. It is commonly referred to as Adipocyte-specific secretory factor (ADSF), Fizz3, RSTN, or cysteine-rich protein 1(XCP1). The normal physiological range of resistin in human serum so observed is 7–22 ng/mL. Circulatory resistin is shown to oligomerize to higher-order structures and is up-regulated in some autoimmune disorders, metabolic diseases as well as in cancerous conditions.

The immature resistin protein in humans consists of 108 amino acids whereas in rodents it was observed to be slightly longer with 114 amino acids. Human and mice resistin exhibit only 59% similarity in their sequence, and differ significantly in their secondary structures. Resistin so observed in humans is mostly monocytes. This cells on being stimulated by pro-inflammatory mediators enable resistin to mediate the recruitment of other immune cells. This elevated level of resistin is often associated with chronic low-grade sub-clinical inflammation accompanied with obesity which involves macrophage infiltration in the adipose tissues. Moreover, human resistin also promotes the production of numerous inflammatory molecules like VCAM-1, ICAM-1 and MCP-1. Additionally, resistin activates p38 MAPK signaling pathway which impairs insulin signaling and alters oxidative stress response as well as cell proliferation. Precursor human resistin forms a mature molecule of 12.5 kDa and it mainly exists in two conformations:

- Trimer with a molecular weight of 45 kDa
- Oligomer with a molecular weight of 660 kDa

The assembly of these trimers and oligomers promotes secretion of TNF-α, IL-6, IL-8, IL-12 and IL-1β, generates reactive oxygen species (ROS) and inhibits eNOS.

**Abbreviations:** RELM, Resistin like molecule; ROS, Reactive oxygen species; CAP1, Adenylyl cyclase associated protein 1; ROR1, Receptor Tyrosine like Orphan Receptor 1; TLR4, Toll-like receptor 4; LPS, Lipopolysaccharide; CAD, Coronary Artery Disease; BMI, Body Mass Index; EPC, Endothelial Progenitor cells; EMT, Epithelial to Mesenchymal transition; LDL, Low density lipoprotein; LDLR, Low density lipoprotein receptor; PCSK9, Proprotein subtilisin kexin type 9; NAFLD, Non-alcoholic fatty liver disease; DTIC, Dacarbazine.

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Mouse resistin is 11 kDa polypeptide. Several factors like glucocorticoids, growth hormones, testosterone and prolactin upregulate resistin in rat and mouse adipose cells, whereas insulin, epinephrine and somatotropin suppress its secretion. High serum resistin in rodents alter glucose homeostasis and insulin resistance in liver and skeletal muscle by impairing AMPK. Reports suggest secretion of resistin in rodents is influenced by genetics as well as diet. Moreover, it has been reported that resistin increases in animals in response to hyperglycemia and promotes hepatic glucose production as well. As resistin exerts different regulatory mechanisms, assigning biological properties to rodent resistin remains obscure.

Resistin structure

Unraveling the structure of a molecule facilitates a better understanding of its structure-function relationship. The crystal structure of resistin and RELM-β was first determined by Patel et al. which revealed an unusual multimeric structure with each protomer consisting of carboxy-terminal disulfide-rich β-sheets as a ‘head’ domain and an amino-terminal alpha-helical region as ‘tail’ domain. Three-stranded coiled coils have been reported to form by an association of the alpha-helical segment while the formation of a tail to tail hexamers are mediated by surface exposed interchain disulfide linkages. Structure of RELM-γ is very closely related to RELM-α but with varied tissue expression profiles. The secondary structure of human resistin was observed to be rich in α-helices whereas mice resistin mostly consists of β-sheets.

There are three subtypes of RELMs identified till date:

a) RELM-α or FIZZ1 is a secretory protein primarily present in the adipose tissue, which functions as a pro-inflammatory cytokine during murine allergic pulmonary inflammation. It is also detected in several pulmonary infections as well as in lung cells during fibrosis. Additionally, it has been observed to induce Th2 cytokine immune responses which negatively regulates Th2 responses in pulmonary granuloma formation by helminth parasites. FIZZ1 has been recognized as one of the main signatures of M2 or alternatively activated macrophages. Moreover, RELM-α is also involved in repair of tissues and promotes fibrosis by stimulating Th2 cytokines.

b) RELM-β, also known as FIZZ2, is mainly present in the goblet and epithelial cells of the gastrointestinal tract and promotes the proliferative capacity of the cells. It has also been reported to function as a chemotactant for bone marrow cells, with a major focus on the bone-marrow derived CD11C+ dendritic cells. The human ortholog of FIZZ2 shows significant sequence homology to both rodent FIZZ2 and FIZZ1. Additionally, increased expression of RELM-β is observed in the Airways of asthmatic patients wherein it regulates airway epithelial function. This establishes its role in pulmonary remodeling. It has also been reported to induce proliferation by enhancing expression of MUCSAC, ERK, MAPK, and PI3/Akt pathway, including TGFβ, EGF and VEGF. RELM-β plays contributory roles in metabolic dysfunction by suppressing insulin signaling in hepatocytes and activating MAPK pathway. Owing to its anti-microbial activity, both mouse and human RELM-β bind and permeabilize the membrane of gram-negative bacteria, thus acting on the pathogen and on the host.

c) RELM-γ is the least studied protein amongst the three and is expressed in white blood cells, spleen, thymus as well as the nasal respiratory epithelium of cigarette smoked rats. It mainly exhibits cytokine-like functions in the hematopoietic tissues. It was also observed to interact with human neutrophil alpha-defensin and plays a pivotal role in the chemotaxis of bone-marrow-derived myeloid cells.

Source

The sources of resistin are immune and epithelial cells, including peripheral blood mononuclear (PBMCs), macrophages and bone marrow cells, primarily in primates, pigs and dogs, while in rodents the main source is adipose tissue. Numerous literature indicate that resistin expression is not only restricted to adipose tissue but also detected in the stomach, small and large intestine, adrenal gland and skeletal muscle. Expression of resistin mRNA varies according to the deposition of white adipose tissue and gender specificity- the highest level being observed in female gonadal fat.

Receptors

CAP1, Decorin, ROR1 and TLR4 have been identified as receptors for resistin which causes activation of different signaling cascades.

a) ROR1 - ROR1 or Receptor Tyrosine like Orphan Receptor 1 is mostly expressed in 3T3-L1 preadipocytes which facilitate glucose uptake, adipogenesis, as well as development of the nervous system in embryonic stages.

b) CAP1 - One of the receptors of resistin present on monocytes is CAP1. It is an actin-binding protein found mainly in the cytosol. It regulates filamentous dynamics and activates the cyclic AMP pathway. Resistin is reported to bind directly to CAP1 in monocytes and upregulate cAMP, PKA and NFκB dependent transcription of inflammatory cytokines.

c) Decorin - Resistin has been reported to bind to Decorin, a member of the leucine-rich proteoglycan family present on adipocytes. On binding with Decorin, it regulates WAT (White adipose tissue) expansion as well promotes proliferation and migration of 3T3-L1 cells.

d) TLR4 - Additionally, TLR4 or Toll-like receptor 4 has been identified as one of the receptors from the TLRs. These receptors belong to type I transmembrane protein family but differ in their ligand specificity as well as their presence in different organisms. Resistin competes with LPS for binding to TLR4 which activates the Renin-angiotensin system via TLR4/p65/Agt pathway and induces hypertension. Direct binding of human resistin to TLR4 in the hypothalamus also causes activation of pro-inflammatory pathways and metastasis in cancerous conditions.

Functions

Several other functions such as blood glucose and lipid metabolism, modulation of satiety centers in hypothalamus and pituitary somatotrophic cells, central nervous system regulation, synthesis and secretion of different pro-inflammatory cytokines and differentiation of monocytes into macrophages, control of heart contractility, angiogenesis, smooth muscle cell activity, renal functioning and bone remodeling have been attributed to resistin. For years, resistin has also been identified to play significant roles in various diseases too (Fig. 1).

The review mainly highlights the roles of resistin in a) Cancer, b) Immunological disorders and c) Metabolic disorders. (Fig. 2).

Resistin in cancer

Cancer is one of the most prevalent as well as life-threatening diseases worldwide. Pre-clinical and clinical studies indicated the presence of a high level of serum resistin in patients with various cancers. Interestingly, elevated resistin level is not only predominantly exhibited in obesity-influenced cancers i.e. breast, colon, etc. but also in cancers irrespective of obesity such as in lung, renal, etc. Resistin has been linked to increased risk of progression, angiogenesis and metastasis in various cancer models (Fig. 3). Its role has been also associated with chemoresistance and stemness induction in cancer, yet related
mechanistic details need further exploration.82

Resistin as biomarker

Biomarker is a measurable characteristic of the pathophysiological condition of an individual, which can be useful in early diagnosis and understanding the therapeutic regime for any disease.83 Evidences suggest resistin as a potential prognostic and diagnostic biomarker in cancer.84

A diverse array of studies depicts high serum resistin levels in patients of breast cancer, lymphoma, esophageal squamous cell carcinoma, endometrial adenocarcinoma, gastric and colorectal cancer.85 Study done in 80 breast cancer patients and 50 healthy control indicated increased resistin levels in breast cancer patients compared to control. Moreover, patients with lymph node metastasis were also reported to have increased resistin level when compared with the non-lymph node metastatic patients.86 The relationship between a high level of resistin and increased risk of breast cancer has been observed to be independent of age, status of menopause, serum glucose, BMI and adiponectin. However, it is significantly associated with tumor and inflammatory markers, tumor size, cancer grade, stage and lymph node invasion.83,85

Another case-control study involving 37 Caucasian endometrial female patients and 39 healthy controls who were BMI and age matched, revealed a significant difference in resistin level between the patients and the control group. The mean resistin level was observed to be 24.2 ng/ml in the affected individuals. Whereas, the level was found to be much less in healthy individuals (10.1 ng/ml).84 However the exact role of this elevated resistin in various cancers is yet to be explored.

Resistin in proliferation and arrest

Signaling pathways that link resistin with cancer include TLR4, PI-3 K, and NFκB. In several cancers activation of diverse signaling pathways has been associated with proliferation. In prostate cancer, progression takes place via AKT pathway whereas in lung cancer it is mainly through PI-3 K, NFκB, EGFR and TLR4 receptor.86,87 Few reports have indicated that proliferation in melanoma by resistin is mediated by pAKT and Cav-1, whereas in breast cancer progression has been attributed to IL-6 dependent STAT 3 signaling.88,89 Resistin-induced progression in ovarian cancer has been observed to be mostly via miR let-7a, miR-200c and miR-186.90 Yet, in gastric cancer cells resistin and visfatin synergistically increase cell proliferation by activating the expression of the telomerase gene.90 A similar report suggests upregulation of Human Telomerase Reverse Transcriptase (hTERT) by resistin treatment only.91
Recent studies suggest silencing of CAP1 along with TLR4 decreases proliferation of pancreatic cell lines mediated by STAT3, both in vitro and in vivo.\(^92\) Interestingly, another report implicates resistin’s role in cell cycle arrest in colon cancer cells by upregulation of SOCS3.\(^79\) Numerous unambiguous explorations of resistin on the proliferation of cancer cells have opened up avenues for more detailed studies in the future.

Resistin in angiogenesis

Reports suggest resistin induces angiogenesis by regulating various pathways. Evidences indicate in chondrosarcoma cells, it induces VEGF-A expression through PI3K and Akt signaling pathway and downregulates microRNA expression (miR)–16–5p resulting in increased angiogenesis.\(^69\) Whereas, in ovarian cancer cell (HO-8910) resistin-induced expression of VEGF takes place through the PI3K/Akt-Sp1 pathway.\(^54\) According to available literature, resistin induces SDF-1 expression and promotes angiogenesis in human gastric cancer cells.\(^90\) However ERK, JNK and p38 pathways are mostly responsible for inducing VEGF mediated angiogenesis in osteocarcinoma cells.\(^96\) Inhibition of these signaling molecules reduce expression of VEGF-A and subsequently causes a decrease in EPC migration and tube formation.\(^80\)

Resistin in metastasis

Metastasis is one of the main causes of cancer-related deaths worldwide. A comparative study including 42 endometrial cancer patients and 42 control individuals suggest high serum resistin level in endometrial patients.\(^97\) Similar studies with gastroesophageal cancer and postmenopausal breast cancer patients depict higher resistin levels in patients with distant metastasis.\(^79,90\) In breast cancer cells resistin induces phosphorylation of c-src, PP2A, PKCe, ezrin, radixin, moesin as well as increases expression of vimentin promoting cell invasion and metastasis of breast cancer cell.\(^79\) Resistin treatment also resulted in increased cell invasion and MMP-2 expression through AMPK and p38 pathway while suppressing mir 519d.\(^95\) However, on being treated with resistin, ovarian cancer cells A2780 and SK-OV-3 secrete reduced levels of E-cadherin and enhanced levels of vimentin and ZEB1 resulting in EMT transition.\(^80\) Whereas Src/EGFR, NFKB, PI3K were also observed to be involved in signaling for invasion and migration in lung cancer cells upon resistin exposure.\(^97\) For the first time it has been demonstrated that tumor-associated dendritic cells (TADCs) of lung cancer, secrete resistin and treatment of condition media from TADCs upregulates Twist, an inducer of EMT.\(^100\) Strategies for targeting signaling molecules induced by resistin have been devised (Table 1).

Resistin and its effect on chemotherapy

Amongst several multifaceted roles of resistin, the least explored area has been its role in imparting therapeutic resistance. Few reports suggest resistin’s involvement in promoting resistance towards different anticancer, antimitabolic or immunomodulatory drugs. Numerous factors contribute to this resistance such as impaired immune response, alterations in metabolic profile, inducing stemness, etc. Studies reported that increased resistin level induces chemoresistance to Gemicabtine in pancreatic cancer whereas resistin exposed breast cancer promotes resistance to Doxorubicin.\(^93,101,102\) It has also been shown that resistin abrogates doxorubicin-induced cell death through autophagy induction by activation of AMPK/mTOR/ULK1 and JNK signaling pathways.\(^103\) Studies in ovarian cancer have reported a significant correlation between high resistin level and poor prognosis. Additionally, it promotes chemoresistance to cisplatin by increasing stemness of ovarian cancer cells. Resistin is also known to induce chemoresistance in ovarian cancer by suppressing miRNAs let-7, mir-200c and mir-186.\(^104\)

Interestingly, a recent report suggests that treating colon cancer cells with exogenous resistin make them resistant to 5-fluorouracil because of the decreased drug uptake which is caused due to the arrest of cells in the G1 phase.\(^90\) Moreover, Fang et.al., reported that resistin inhibits chemotherapy-induced cleavage of caspases by the activation of NFKB and PI3K/Akt pathways in multiple myeloma. It decreases the expression of both DNA methyltransferases DNMT1 and DNMT3a as well as the methylation of ATP binding cassette (ABC) gene promoters which in turn increases the expression and the drug efflux function of ABC transporters in myeloma cells.\(^102\) Another recent study from our lab also demonstrates resistin impairs the efficacy of DTIC in melanoma by
increasing and stabilizing the protein levels of Cav-1 and P-gp.

From the available literature, it is evident that resistin is one of the key factors in imparting chemoresistance to various therapeutic interventions. However, detailed systemic and clinical studies are required to understand the mechanism underlying this phenomenon. The role of resistin in intervening chemotherapeutic responses should be investigated to elucidate the mode of action through which resistin impedes the efficacy of various drugs directly or indirectly.

Resistin in immunological disorders

Resistin being a pro-inflammatory cytokine, also plays a significant role in modulating immune functions in pathological conditions. It alters the secretory profile of factors like Interleukin-1 and Interleukin-6, which are key factors in imparting chemoresistance to various therapeutic interventions. However, detailed systemic and clinical studies are required to understand the mechanism underlying this phenomenon. The role of resistin in intervening chemotherapeutic responses should be investigated to elucidate the mode of action through which resistin impedes the efficacy of various drugs directly or indirectly.

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Resistin in immunological disorders
a) Sepsis- A study involving 95 patients of the Intensive Care Unit at Karolinska University Hospital and Center for Infectious Medicine, Karolinska Institute, Huddinge, Sweden, reported that resistin is elevated in patients suffering from sepsis or septic shock. It was the first report for establishing resistin as a biomarker for the severity of the disease as well as prolonged inflammatory state of critically ill patients.\(^{113}\) Sepsis-induced immunosuppression is a key factor contributing to morbidity and mortality of critically ill patients and polymorphonuclear neutrophil dysfunction is believed to be a hallmark of this immunosuppression.\(^{114}\)

b) Rheumatoid arthritis- Several studies have reported increased levels of resistin in the synovial fluid of rheumatoid arthritis patients. Evidence shows that it increases osteoclastogenesis which induces a weak differentiation of pre-osteoblasts into osteoblasts.\(^{2}\) Resistin has been observed to increase the pathogenesis of rheumatoid arthritis by inducing the production of chemokines like CXCL1, CXCL2, CXCL3, CXCL5, CXCL6 and CXCL8.\(^{115}\) Resistin has been reported to co-localize with macrophages, B lymphocytes and plasma cells suggesting a pathogenicity of resistin in arthritis condition.\(^{116}\)

c) Inflammatory disorder- Besides stimulating the production of numerous pro-inflammatory cytokines, resistin activates signal transduction pathways like p38, JNK and ERK.\(^{95}\) It activates ERK pathway inducing proliferation of smooth muscle which in turn affects vascular restenosis.\(^{65}\) Resistin inhibits eNOS gene expression and induces oxidative stress.\(^{117}\)

Cardiovascular disorder

Despite reports demonstrating resistin being an important predictor of cardiovascular diseases, still, its relation remains controversial. In 2005, Reilly and his colleagues did the first landmark experiment to correlate elevated resistin level with a surrogate marker in atherosclerosis patients-coronary-calcium score.\(^{118}\) Reports suggest in patients with stable CAD, a stepwise increase in the resistin level can be observed with >50% stenosed coronary vessel.\(^{119}\) Moreover, resistin has been observed to play a major predictor in atherosclerosis (ATS) and related cardiovascular diseases such as myocardial infarction, heart failure and cardiac ischemic events.\(^{12,23,118,120-124}\) Hyper-resistinemia state also increases the incidence of cardiovascular diseases even with a deregulated ischemia-perfusion injury, reduced contractility and hypertrophy.\(^{66,125}\) In women’s health initiative observational study, elevated resistin level was strongly correlated with increased ischemic stroke in post-menopausal women.\(^{126}\) Frenkel et.al also performed a Framingham offspring study where a 26% increase in heart failure was observed with each 7.45 ng/ml increase in resistin level in serum.\(^{17}\) In vitro studies have shown high resistin level to induce various pro-atherogenic molecules like ET-1, VCAM-1 and MCP-1 and downregulate anti-atherogenic molecules like TRAF-3 which is an inhibitor of CD40 signaling in endothelial cells.\(^{128}\) Additionally, resistin contributes to the impairment of glucose uptake in cardiomyocytes which alters vesicle trafficking.\(^{129}\) Furthermore, resistin is observed in diabetic hearts, promoting cardiac hypertrophy, and decreasing myocyte contractility.\(^{130}\) Aortic stenosis is also a cardiac disorder associated with a high resistin condition which leads to an elevated vulvular calcium deposition and increased concentration of macrophages.\(^{2,5,118,123}\) However, the effect of resistin in human heart failure and aggravation should be explored in detail.

Resistin with metabolic disorders

As stated earlier, resistin was first discovered by Steppan et.al. as a link between diabetes and obesity by imparting insulin resistance\(^1\). Reports suggest a correlation between increased resistin expression with various metabolic disorders since past few decades. Fig 4 summarizes mechanisms exhibited by resistin in these metabolic disorders.

Obesity

Few studies previously reported that resistin levels increase in diet-induced obese mouse but its role in obesity remains largely obscure.\(^{88}\) Also, there is an increase in adipose tissue and macrophages which secrete resistin in obese conditions.\(^{131}\) The obesity and low-grade chronic inflammation are synchronous in nature.\(^{125}\) In a study of 169
Cyclolepis genistoides is a phytochemical known to modulate the non-obese (mean body mass index [BMI] = 24.51–3.69 kg/m²) and 160 obese (mean BMI = 36–4.78 kg/m²) subjects, serum resistin levels were significantly associated with BMI (P = .047). Besides serum levels, the tissue-specific expression of resistin is dependent on various factors. It was observed that fasting downregulates resistin gene expression in adipose and pituitary tissue, but not in the hypothalamus. Resistin mRNA was decreased under starvation whereas it was up-regulated with an increase in visceral fat. Contrastingly, the pituitary levels of resistin were decreased in presence of both high (ob/ob) and low (fasting) adipose stores which are dependent on age and gender. In another study, resistin level was statistically correlated with insulin, BMI, body-fat content and homeostasis model assessment (HOMA). However it is an established fact that obesity has close relations with immune cells especially with macrophages- (a) the increased fat accumulation concomitant with infiltration, (b) polarization (c) and in-situ proliferation of macrophages. It was characterized that CAP1 serves as the receptor for resistin in white adipose tissues of resistin humanized mice. However, the expression of CAP1 in adipose resident immune cells and the role of resistin is still an unexplored area. Surprisingly, resistin is also known to inhibit adipocyte differentiation and can function as a feedback regulator for adipogenesis. Moreover, the resistin mRNA and protein levels in ob/ob mice, (genetically obese mouse model), are suppressed by exogenous leptin treatment. These observations portray the highly contrasting role of resistin in disorders such as obesity and diabetes. The treatment of LPS and zymosan to human subcutaneous adipocytes increases secretion of resistin whereas treatment of human recombinant resistin in these cells significantly increases stimulation of TLR-2, IKKβ and JNK. The treatment of preadipocytes with PPARγ agonist GW501516 induces expression of PPARγ and resistin. Cyclolepis genistoides is a phytochemical known to modulate the expression of PPARγ and downregulate resistin. The treatment of chromium picolenate is also known to inhibit resistin secretion in insulin resistant and normal 3T3-L1 adipocytes by inhibiting AMPK. Strategies to target resistin in obesity are summarized in Table 2.

Diabetes

In the past few decades, resistin has been reported to play a significant role in Type 2 Diabetes Mellitus (T2DM). Insulin resistance is an important phenomenon exhibited in obese phenotype, which if manifested for extended time periods may lead to glucose intolerance and hyperglycemia. Several evidences suggest a strong correlation between resistin and obesity-associated diabetes. It is known to regulate glucose homeostasis and antagonizes hepatic insulin action. Exogenous resistin administration in mice causes an increase in glucose production and blood glucose levels. The renal alteration in diabetes is one of the complications which takes place and was observed to be negatively correlated to serum resistin level. Over-expression of resistin in L6 rat myotubes inhibits insulin-stimulated 2-Deoxy glucose uptake without affecting GLUT4 translocation, GLUT1 expression, and IRS signaling. The infusion of resistin or resistin-like molecule RELMα induces hepatic insulin resistance which was denoted by increased hepatic glucose production in Adult male Sprague Dawley rats. The treatment of resistin in rat hepatocyte and mice with liver-specific resistin expression impair hepatic insulin action by decreasing phosphorylation of GSK3β at ser 9. A study was done in C57BL/6 J mice has reported that treatment of resistin decreases the storage of glycogen by increased expression of p65 which binds with the promoter of keratin 8 (K8) and increase its expression. In a case-control study it was observed that 68 + G to A phenotype of RETN may increase susceptibility to T2DM in the Thai population. Drugs to target resistin in Diabetes have been deduced.

| Table 2 |
|---|
| **Anti-obesity drugs affecting resistin levels.** |
| Serial no. | Drug name | Phase | NCT no./PMID |
| 1. | Metformin | Clinical trials | NCT02438540 |
| 2. | Entacapone | Phase 1 | NCT02349243 |
| 3. | Ezetimibe add on to statin therapy | Clinical trials in obese patients with atherosclerosis | NCT00485121 |
| 4. | Dapagliflozin, Metformin | Phase 2 | NCT03968224 |
| 5. | Losartan + Simvastatin | Phase 3 | NCT00669435 |
| 6. | Olmitast | Clinical Tests approved | 21,812,797 |

## Hypercholesterolemia

Several studies show a positive correlation of resistin with free cholesterol as well as LDL (Low-Density Lipoprotein) cholesterol. Increased ROS production and lipid accumulation in the intima of the vessels enhances hyper resistinemia. Monocytes which produce resistin and become macrophages are recruited- these subsequently take up cholesterol and become foam cells. Resistin is mainly observed to increase lipid accumulation as well as oxLDL in human macrophages accompanied by increased CD36 expression at both protein and mRNA level. Abrogating resistin in obese mice decreases hepatic steatosis, serum cholesterol as well as VLDL secretion which is a consequence of the reduced expression of genes involved in hepatic lipogenesis and VLDL export. NAFLD condition has also been associated with increase serum resistin level. Resistin has been observed to stimulate PCK9, by enhanced gene expression and protein stability which leads to degradation of low-density lipoprotein receptor by 40%. Over-expression of resistin induces dyslipidemic condition by decreasing LDLR and Apolipoprotein A1 in the liver partially through enhanced secretion of lipoprotein. Whereas, in skeletal muscles, resistin induces FATP1 expression and decreases phosphorylation of AMPK and ACC promoting lipid accumulation. Interestingly, it has been reported that, in patients suffering from atherosclerosis, Pitavastatin significantly decreases hypercholesterolemia along with serum resistin and C-reactive protein. Strategies to target resistin in hypercholesterolemic condition has been enlisted (Table 4).

## Conclusion

With an increase in the sedentary lifestyle as well as epigenetic changes, incidences of pathological disorders are on the rise. Available evidences suggest a positive correlation between high resistin level and certain chronic diseases. Accumulative observations indicate that resistin might play a pivotal role in aggravating various disorders, which may contribute to increase in the mortality rate in subjects with pre-existing comorbidities. But the relation is still poorly understood. Additionally, from a molecular perspective, resistin has been reported to be involved in the regulation of several signaling pathways which include IGF-1, NFκB, STAT, MAPK, PI3K etc. as well as some genetic recombination or polymorphisms. Further investigation will aid in

| Table 3 |
|---|
| **Anti-diabetic drugs affecting resistin levels.** |
| Serial no. | Drug name | Phase | NCT no./PMID |
| 1. | Metformin | Phase 1 | NCT01396564 |
| 2. | Pioglitazone | Phase 2 | NCT01223196 |
| 3. | Rosiglitazone | Intervventional clinical trial | NCT00486187 |
| 4. | Metformin/sulfonylurea | Phase 3 | NCT01386671 |
| 5. | Metformin glycanate | Phase 2 | NCT02330549 |
| 6. | Liraglutide | Clinical trial | NCT02775266 |
| 7. | Alpha lipoic acid | Intervventional Clinical trial | NCT02138045 |
| 8. | Cenicriviroc 150 mg | Phase 4 | NCT00669435 |
understanding the complexity of resistin in these clinical disorders. This review along with recent literature has laid out the ground work for resistin’s roles as a putative hallmark in numerous pathological disorders because of its varied roles in inflammation, regulating metabolism as well as in cancer. In cancers, resistin influences various hallmarks of cancers including chemotherapeutic responses. In conclusion, the comprehensive information of resistin in various pathological disorders represents an extensive area of research for targeting resistin as a diagnostic and prognostic tool which would help in better understanding its relevance in these comorbidities.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Author Contributions

Ankita Deb: Conceptualization, data research, literature survey, writing-original draft preparation, discussion of the content, writing-reviewing, editing, generation of figures and tables. Bhavana Deshmukh: Data research, literature survey, writing-reviewing, editing, generating of tables. Pranay Ramteke: Data research, literature survey, writing-reviewing and editing. Manoj Kumar Bhat: Conceptualization, supervision, discussion of the content, writing-reviewing and editing. All the authors read and approved the manuscript before submission.

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Table 4

| Serial no. | Drug name | Phase | NCT no. | PMID |
|-----------|-----------|-------|---------|------|
| 1. | Pitavastatin | Clinical study | 18,385,536 | |
| 2. | PCSK9 monoclonal antibodies (AMG145, REGN727) | Phase 1 and 2 | 24,217,159 | |
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