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Chitinase 3 Like-1: An Emerging Molecule Involved in Diabetes and Diabetic Complications

Michelino Di Rosa Lucia Malaguarnera

Department of Biomedical and Biotechnological Sciences, School of Medicine, University of Catania, Catania, Italy

Key Words

Diabetes mellitus · Chitinase 3 like-1 · Endothelial dysfunction · Macrophage activation · Inflammation · Diabetic complications

Abstract

Chitinase 3 like-1 (CHI3L1) is a chitinase-like protein member of family 18 chitinases, expressed in innate immune cells and involved in endothelial dysfunction and tissue remodelling. Since CHI3L1 is highly expressed in a variety of inflammatory diseases of infectious and non-infectious aetiology, it is recognised as a non-invasive prognostic biomarker for inflammation. A variety of studies revealing the increase in CHI3L1 levels in obesity, insulin resistance and in pathological conditions, such as atherosclerosis, coronary artery disease, acute ischaemic stroke, nephropathy, diabetic retinopathy and osteolytic processes, have suggested that CHI3L1 may also play a critical role in the evolution and complication of diabetes mellitus (DM). In this review we highlight the impact of CHI3L1 expression in DM and its contribution to the complication of this disease.

Introduction

Diabetes mellitus (DM) is distinguished by metabolic defects resulting from dysfunction in the glucose-handling machinery of the body. It arises in two major forms. Type 1 DM (T1DM), which is the most common form of DM in children, may have an autoimmune or post-infectious aetiology and is caused by a decrease in insulin, which regulates glucose metabolism. Type 2 DM (T2DM) typically involves insulin resistance (IR) at the cellular level and comprises the majority of adult-onset DM. T2DM may rarely occur in children. The metabolic defects of DM are common in all forms of the disease. The reduction of insulin activity causes persistent hyperglycaemia, which leads to osmotic and oxidative stress and results in injury to the nerves, kidneys, eyes, liver, articular cartilage and other tissues. The pathophysiology of DM involves genetics, epigenetics and environmental factors, together with immune disturbance [1–3]. The absence of physical activity in combination with excess calorie intake leads to obesity and autoimmunity onset in developed societies [3]. Obesity is reaching epidemic proportions and is one of the most important chronic diseases leading to an increased risk for several metabolic complications. The dietary habits in Western societies and a high body mass index (BMI) constitute risk factors for autoimmune diseases [4]. Adipose tissue represents a

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Lucia Malaguarnera
Department of Biomedical and Biotechnological Sciences
University of Catania
IT–95124 Catania (Italy)
E-Mail lucmal@unict.it

complex and highly active metabolic and endocrine organ [5] and plays a key role in the pathogenesis of IR through several released molecules that can affect different steps in insulin action. IR is the most common metabolic alteration associated with obesity, which in turn generates other metabolic diseases as well as cardiovascular complications [6]. Obesity induces a state of chronic low-grade inflammation because of the circulating levels of markers of inflammation, including both pro-inflammatory cytokines and acute-phase proteins [7]. In response to environmental stresses, macrophages, endothelial cells and adipocytes release inflammatory cytokines, including the interleukins (IL)-1, IL-6, tumour necrosis factor-α (TNF-α), and chemokines that, in turn, induce the production of acute-phase proteins, such as C-reactive protein (CRP) and amyloid deposition in the pancreas [8]. The cellular stresses, such as oxidative stress, ER stress, lipotoxicity and glucotoxicity, exacerbate IR, islet β-cell dysfunction and induce the inflammatory response that is related to this pathophysiological state. In this context, increasing evidence indicates that chitinase 3-like 1 (CHI3L1), a member of the chitinases family, is also involved also in the pathogenesis of DM [9, 10]. Exaggerated production of CHI3L1 could cause unexpected pathogenic effects in human tissues, directly initiating and perpetuating chronic inflammation. This review considers the relationship between CHI3L1 and DM and its contribution in the complications of this disease.

CHI3L1 Biological Activities

CHI3L1 protein – also called YLK-40, based on its three N-terminal amino acids: tyrosine (Y), lysine (K) and leucine (L) – is a heparin-, chitin- and collagen-binding glycoprotein that was originally discovered in mouse breast cancer cells [11]. CHI3L1 is a member of the protein family of chi-lectins (chitinase-like lectins) [12]. The members of this protein family are structurally related to the 18 glycohydrolase family. On the basis of a substitution of the catalytic essential glutamic acid residue in the active site of this protein, CHI3L1 has no enzymatic activity [13]. Biological activities of CHI3L1 embrace the regulation of cell proliferation, adhesion, migration and activation. CHI3L1 is produced by a variety of cells, including neutrophils, monocytes/macrophages, monocyte-derived dendritic cells, osteoclasts, chondrocytes, fibroblasts, vascular smooth muscle cells and endothelial cells [12, 14–16]. Local inflamed tissues, including adipose tissues in T2DM, produce CHI3L1 locally [17]. In addition, CHI3L1 stimulating the production of inflammatory mediators (e.g. CCL2, CXCL2, MMP-9) [17] acts as a pro-inflammatory biomarker [18]. Induction of CHI3L1 has been reported in patients suffering from a surprisingly vast array of diseases, including a number of autoimmune disorders [11]. Circulating levels of CHI3L1 are increased in patients with T2DM and positively correlate with IR [19]. In addition, elevated plasma levels of CHI3L1 have been found in liver fibrosis [20], rheumatoid arthritis, atherosclerosis, coronary artery disease, Alzheimer's disease and inflammation-related illnesses in humans [18, 21, 22]. High CHI3L1 levels are predictors of overall and cardiovascular mortality [23]. The expression of CHI3L1 has been shown to be regulated by various pro-inflammatory cytokines, including IL-6, interferon-γ (IFN-γ), IL-1β and TNF-α [24]. Therefore, CHI3L1 can be regarded as an acute-phase reactant associated with disease severity and mortality in a variety of infections. Additionally, CHI3L1 stimulates the growth of fibroblast cells [23], promotes proliferation and antagonizes catabolic or degradative processes during the inflammatory response of connective tissues [25], activates the protein kinase B (AKT) and phosphoinositide-3 kinase (PI3K) signalling pathway, and exerts anti-apoptotic [26] and angiogenic function [27] (fig. 1). CHI3L1 plays a crucial role not only during innate but also in acquired immunity [28, 29]. Cellular receptors mediating its biological effects have not been identified; however, its regulation by IL-6 and TNF-α requires sustained activation of the nuclear factor-kappa B (NF-κB), and can bind to collagen types I–III [30]. The ability of CHI3L1 to regulate cell proliferation, adhesion, migration and activation, as well as to regulate extracellular matrix assembly, correlates well with an elevated level of CHI3L1 in the sites of chronic inflammation.

The Immune System in the Regulation of the DM Metabolism

The islets from patients with DM exhibit the typical histology of inflamed tissue with infiltration of immune cells, β-cell apoptosis containing islet amyloid polypeptide and decreased insulin staining [31]. Elevated glucose levels are perceived by the inflammasomes [32], which, acting as innate immune sensors, detect metabolic danger signals. The inflammasomes activate caspase-1 that cleaves pro-IL-1β into active IL-1β, which, in turn, binds to its membrane receptor and activates the transcription factor NF-κB, resulting in the production of a wide array

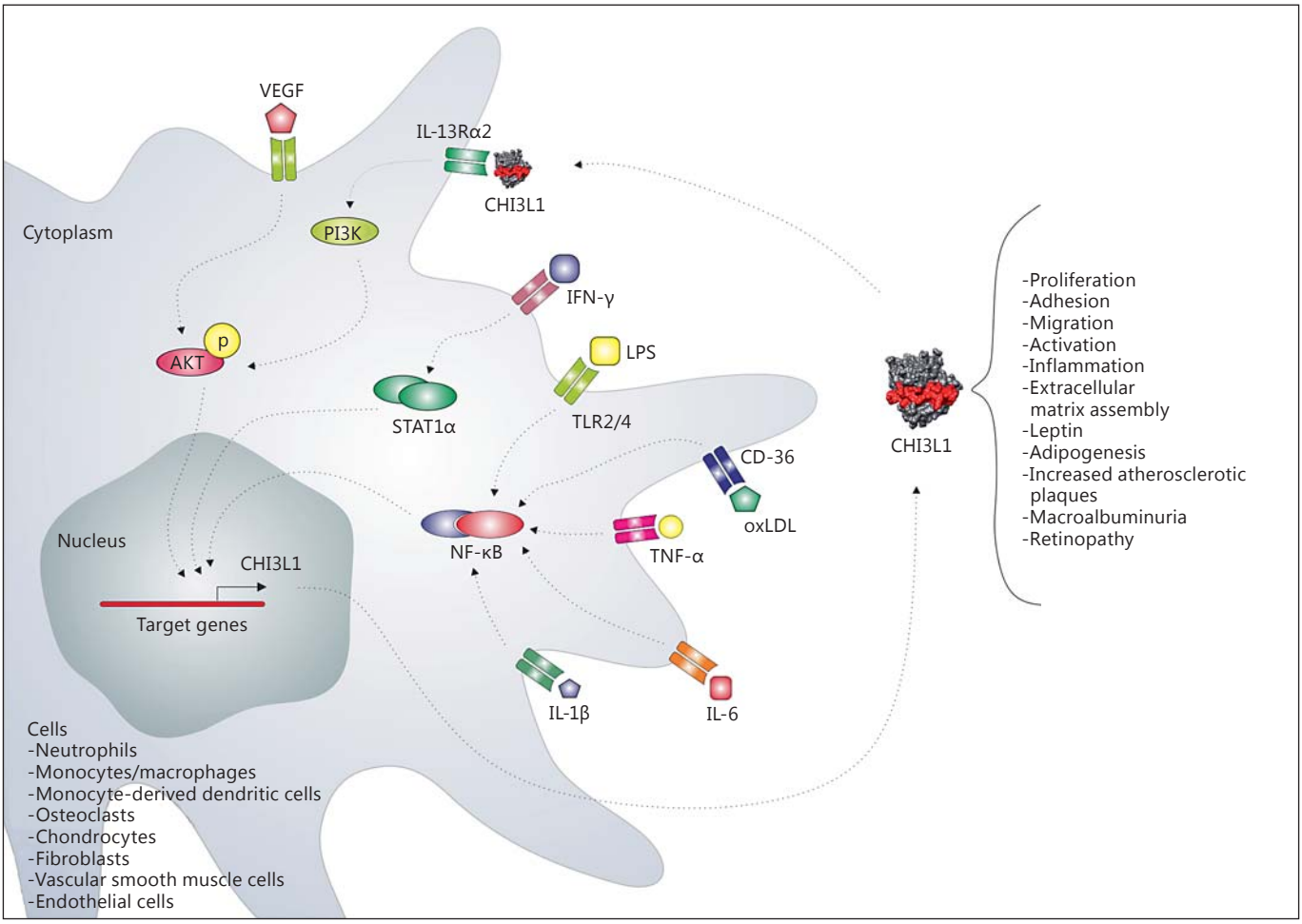

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Fig. 1. The association between CHI3L1 and IR may occur through PI3K, which mediates insulin-stimulated glucose uptake. CHI3L1 binding to a receptor (i.e. IL-13Rα2) is PI3K mediated followed by the phosphorylation of AKT, which leads to CHI3L1 transcription and the ability of CHI3L1 to regulate cell proliferation, adhesion, migration and activation, as well as the regulation of extracellular matrix assembly. The induction and continued secretion of CHI3L1 requires sustained activation of NF-κB by pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) or inflammation mediators (LPS, oxLDL), which in turn enhance CHI3L1 expression.

of cytokines and chemokines, followed by the recruitment of immune cells, including macrophages. While the inflammatory process contributes to defective insulin secretion, the immune system contributes to β-cell adaptation during states of increased insulin demand, which stimulates glucagon-like peptide-1 (GLP-1) secretion from intestinal L-cells and from the pancreatic α-cells [33]. IL-6 particularly mediates cross-talk between insulin-sensitive tissues, L-cells and islets to adapt to variations in insulin demand by increasing L-cell GLP-1 secretion and reprogramming α-cells to process the proglucagon to GLP-1. This endocrine network corroborates the idea of a role for the immune system in the regulation of the metabolism and the importance of the collaborations between α- and β-cells [33]. Therefore, inflammatory mediators, such as IL-1β, IL-6, Toll-like receptors (TLRs), macrophages and chemokines, are elevated in pancreatic islets from patients with DM [34] (fig. 1). Increased glucose concentrations enhance free fatty acid (FFA)-induced expression of inflammatory mediators in both human and mouse islets, suggesting that these responses are probably through an IL-1R/TLR-dependent pathway [34]. FFAs stimulate adipose tissue inflammation through the TLR2 and TLR4 pathways, resulting in IR. The activation of TLR4 in pancreatic β-cells affects insulin secretion in response to glucose in both humans and rodents [35].

Glucose has been shown to induce TLR2 and TLR4 expression via PKC-α and PKC-δ, respectively, by stimulating NADPH oxidase in human monocytes [36]. The state of IR may be enabled by the stimulation of TLR-signalling, as suggested by the findings that TLR2- or TLR4-deficient mice are protected against diet-induced IR compared to wild-type animals [37, 38]. In addition, the in vitro administration of PAMPs specific for TLR2 or TLR4 stimulates an increase in markers of IR [39, 40]. TLR4 is the major intracellular signalling complex for lipopolysaccharide (LPS) [41] (fig. 1). Circulating levels of LPS correlate with insulin levels, glucose and the homoeostatic model assessment of IR (HOMA-IR) [42]. Bolus injections of LPS into healthy human volunteers cause a decrease in the FSIGT (frequently sampled intravenous glucose tolerance) measured insulin sensitivity index [43], indicating that LPS may play a direct role in the progression of IR. Additionally, fetuin-A (FetA), acting as an endogenous ligand for TLR4, plays a crucial role in regulating insulin sensitivity via TLR4 signalling [44]. In FetA knockdown mice, IR caused by a high-fat diet (HFD) resulted in the downregulation of TLR4-mediated inflammatory signalling in adipose tissue, whereas the selective administration of FetA induced inflammatory signalling and IR. Furthermore, it was observed that FFA-induced pro-inflammatory cytokine expression in adipocytes occurred only in the presence of both FetA and TLR4; removing either of them prevented FFA-induced IR [44]. So far, receptors that mediate the effects CHI3L1 have not been defined, and only a potential link between TLR4- and CHI3L1-signalling pathways has been reported [45, 46] (fig. 1).

Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), are pattern recognition receptors (PRRs) similar to TLRs that propagate inflammatory signals in response to peptidoglycan [47]. Therefore, NLRs also play a role in inflammation and IR. This idea was corroborated by the finding that elevated levels of NODs were positively correlated to poor glycaemic control and IR [48]. Remarkably, NOD1/2 double-knockout mice were shown to be protected from HFD-induced IR. In addition, the treatment of 3T3-L1 adipocytes with DAP impaired insulin signalling and glucose uptake, which was reverted by NOD1-specific small interfering RNAs (siRNAs) [49]. Similarly, addition of the NOD2 ligand MDP suppressed basal and insulin-stimulated glucose uptake in L6-GLUT4-myc myotubes [50]. In addition, the elevated expression of NOD1/2 induces the expression of the downstream signalling mediators RIPK2 and NF-κB in monocytes from patients with T2DM [48]. The stimulation of NOD1/2 by their specific bacterial ligands causes the recruitment of RIPK2, a caspase recruitment domain-containing kinase, which then directly binds to Iκβ kinase (IKK-γ) to activate NF-κB for the pro-inflammation response [51] (fig. 1). Moreover, RIPK2 participates in innate immunity specifically by mediating NOD1/2 signalling, but not TLR-mediated immune responses [52]. Another intriguing observation from the study by Shiny et al. [48] was the observation that in monocytes from healthy subjects high glucose enhanced NOD1/2 mRNA expression. Glucose showed a synergistic effect with NOD ligands by augmenting ligand-mediated expression of NOD1/2. Glucose-mediated cellular triggers could be the denominators that differentially regulate PRRs and even contribute to the cross-talk among the different immunomodulators involved in the pro-inflammatory response. Further research is required to determine a possible relationship between PRRs and CHI3L1 overexpression and their role in DM and its complications.

CHI3L1, Obesity and IR

Obesity has profound effects on immunity and inflammation as a critical contributor to the pathogenesis of these metabolic disorders [53, 54]. A high BMI is associated with increased levels of pro-inflammatory cytokines [54]. Different factors are involved in the obesity-related comorbidities, but chronic low-grade inflammation is an emerging responsible element [55]. During obesity, cells from the innate and adaptive immune system infiltrate insulin-sensitive tissues, starting the inflammatory response [56]. Obesity-associated low-grade inflammation results in the persistent stimulation of the immune system mainly characterized by the infiltration of adipose tissue with macrophages [57] that represent the primary source of numerous circulating inflammatory molecules detected in the obese state, and which are fundamental in the development of IR. Consequently, IR results from a combination of altered functions of insulin target cells and the accumulation of macrophages [58]. Thus, both obesity and low-grade inflammation have been linked to the development of IR and T2DM [59]. Plasma levels of acute-phase proteins, white blood cells and pro-inflammatory cytokines are elevated in obese and T2DM patients, whereas these decrease after weight loss [60]. Interestingly, the gene expression profile of peripheral blood mononuclear cells (PBMCs) reflects the visceral fat volume and may be representative of the inflammatory

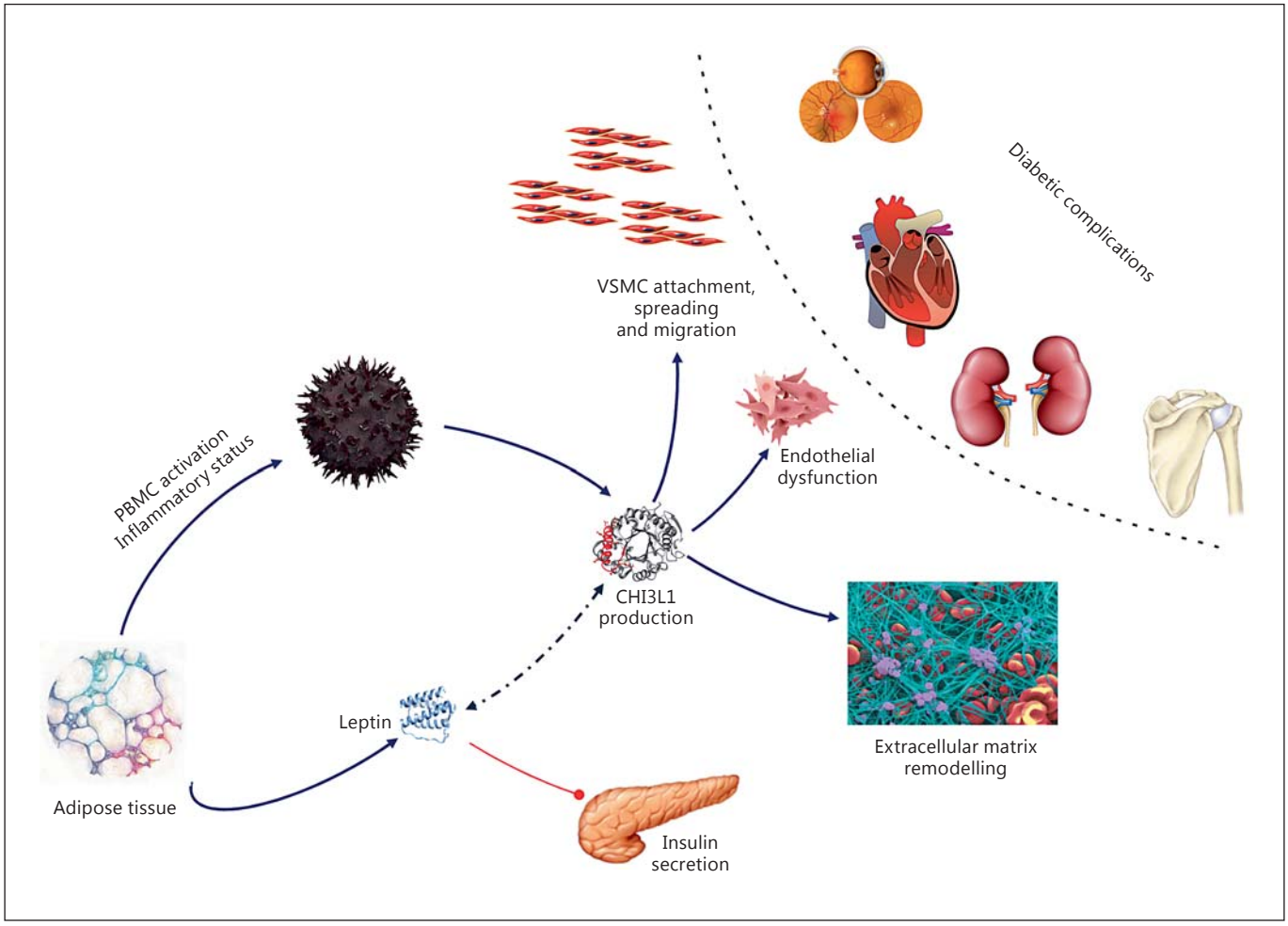

Fig. 2. CHI3L1 expression and diabetic complications.

status in obesity [61]. PBMCs are of great interest and appropriate for research into mechanisms of immune dysfunction in obesity since they are easily available and reflect the responses of dietary modifications, oxidative stress, endogenous lipid mediators and drugs at the gene expression level [61–64]. PBMCs from obese individuals produce elevated levels of TNF-α, IFN-γ and IL-2, whereas the production of the anti-inflammatory cytokine IL-10 is reduced [65]. New factors secreted by adipose tissue promoting inflammatory responses and metabolic dysfunction that have recently been identified include CHI3L1, chemerin, LCN-2 (lipocalin-2) and OPN (osteopontin) [66, 67]. These factors are highly diverse in structure and function. So, whereas OPN and CHI3L1 are directly related to increased inflammation and IR via impaired extracellular matrix remodelling [12, 59], LCN-2 acts as an antagonist to the effect of inflammatory molecules [68]. A recent investigation showed that CHI3L1 is strongly upregulated in obesity independently of the glycaemic state and is associated with different circulating inflammatory markers [66]. CHI3L1 is regulated by an HFD and simultaneously plays an important role in the pathogenesis of asthma and obesity [69]. Elevated CHI3L1 levels are also detectable in obese youth and represent a marker of IR even in childhood [70]. In obesity there is also an increased expression of several chemokine genes in adipose tissue. One of them is MCP-1 (monocyte chemoattractant protein-1), which is predominantly produced in the extracellular space where it primarily acts as a local factor. In addition, MCP-1 influences the function of adipocytes, promotes chemotaxis and the migration of monocytes into the sub-endothelial space, and is an important link between the inflammatory response in adipose tissue and IR [71]. Reportedly, elevated gene expres-

sion levels of CHI3L1 in PBMCs contribute to the worsening of the inflammatory response in obesity. Elevated levels of CHI3L1 have also been reported in the obese prepubertal paediatric population [72], and a significant difference in CHI3L1 levels was found between IR and non-IR subjects [70]. Higher CHI3L1 levels were associated with greater adiposity [73], and a positive correlation between leptin and CHI3L1 levels has been detected in obese subjects, either diabetic or not [73]. Leptin inhibits insulin secretion [74] and, as an adipokine, may represent the missing link between IR and obesity [74] (fig. 2). Systemic low-grade inflammation is related to both circulating and adipose tissue leptin levels in obese women [75]. In addition, CHI3L1 levels were associated with markers of IR, even after adjustment for obesity or inflammation markers [76]. According to different reports, an independent association between CHI3L1 and levels of triglycerides as well as no esterified fatty acids exists [77]. Overall, this evidence strongly confirmed that CHI3L1 is involved in modulating obesity and IR. Therefore, low-grade inflammation and endothelial dysfunction would explain the elevated CHI3L1 levels in diabetic patients. CHI3L1 may be essential in obesity since the association between CHI3L1 and IR may occur through the enzyme PI3K that mediates insulin-stimulated glucose uptake [78]. A crucial signal in the cellular response to CHI3L1 binding to its putative receptor is PI3K-mediated phosphorylation of AKT, which modulates the production of matrix metalloproteinases (MMPs) and chemokines [26]. Moreover, CHI3L1 contributes to the trapping of macrophages into adipose tissue by the inhibition of type I collagenolysis by MMP-1 [26]. Increased CHI3L1 secretion and delivery by its potential receptor might explain its effects on insulin metabolism. The correlation between CHI3L1 and IR could be based on the macrophage infiltration in the adipose tissue. Moreover, it is conceivable that CHI3L1 may contribute to the response to hypoxia in regions of fat depots, as the tissue mass increases during the progressive development of obesity.

CHI3L1 and Diabetes

Subclinical systemic inflammation and changes of a wide variety of inflammatory markers together with the alterations of the metabolic syndrome, including IR, have been found in DM [79, 80]. Rathcke and Vestergaard [81] first reported that CHI3L1 levels increased significantly in T2DM patients. Additionally, they found a correlation between the elevated levels of CHI3L1 and features of dyslipidaemia to be up to 2-fold higher in T2DM patients. Interestingly, the higher plasma CHI3L1 levels in T2DM patients with HOMA-IR suggested that CHI3L1 is associated with IR rather than impaired insulin secretion. Later, other investigations confirmed that T2DM patients have elevated plasma CHI3L1 compared with healthy control subjects [76]. In multivariate regression analysis adjusted for age, sex, fitness, and either plasma TNF-α or fasting plasma glucose, they reported significant associations between plasma CHI3L1, fasting plasma glucose and plasma levels of IL-6, but no associations with parameters of obesity [76]. Successively, elevated CHI3L1 levels were also detected in T1DM patients [82]. The evaluation of this enzyme in relation to other conventional inflammation markers showed that CHI3L1 levels reflect inflammation independently of hsCRP, which is an acute-phase reactant usually elevated in patients with T2DM and positively correlated with increased components of the metabolic syndrome [83], as demonstrated both in T2DM and in chronic heart failure [84]. Some studies showed a correlation between CHI3L1 and glycaemic parameters such as HbA_{1c}, albuminuria [82] and fasting glucose [76]. In concordance with the previous studies performed in T1DM [82, 85], significantly higher concentrations of CHI3L1 and adiponectin were found in T1DM patients from a Mediterranean area with a longer disease evolution but a low atherosclerotic background [86]. A study investigating CHI3L1 in relation to mortality in a population with T2DM demonstrated that high levels CHI3L1 predict all-cause mortality and cardiovascular mortality in these patients [76]. Furthermore, enhanced CHI3L1 levels predict cardiovascular mortality in individuals without known DM or coronary heart disease after adjustment for known cardiovascular risk factors and markers [87, 88]. Interestingly, several studies have documented that single nucleotide polymorphisms of CHI3L1 (rs10399931, –329 G/A, and rs4950928, –131 C/G) are associated with inter-individual CHI3L1 levels and contribute to the susceptibility of different pathological conditions [89–91]. Although a study described an association between a promoter polymorphism of CHI3L1 and levels of low-density lipoprotein (LDL) [92], no consistent association was found between single nucleotide polymorphisms of CHI3L1 and T2DM, IR and dysregulated glucose homoeostasis in a total of 9,438 Danish individuals examined [93]. In view of the aforementioned reports indicating that the increased levels of CHI3L1 in patients with DM correlated with IR, levels of non-esterified fatty acids and triglycerides [94], it is reasonable to assume that CHI3L1 activity may represent a crucial me-

diator playing a detrimental role in mechanisms such as endothelial dysfunction, vascular inflammation and the generation of ROS, which are critical for the progression of diabetes and its complications.

CHI3L1 Atherosclerosis and Cardiovascular Complications

Subclinical inflammation is also involved in the pathogenesis of all stages of atherosclerosis [86], where the induction of acute-phase reactants, proinflammatory cytokines and cell adhesion molecules are associated with the development of myocardial infarction, stroke and peripheral vascular disease, and consequently with cardiovascular mortality [95]. Dysfunction of the endothelium is well known in DM and is the earliest event in atherogenesis, playing a pivotal role in all phases of the atherosclerotic process (from the initiation of the fatty streak to plaque rupture), and is largely responsible for the development of ischaemic heart disease and thrombotic strokes [96]. In human endothelial cells, diabetes influences the modulation of plasminogen activator synthesis by insulin-like growth factor-1 (IGF-1), epidermal growth factor or acidic fibroblast growth factor [97]. The development of IR through a low-grade inflammatory state is influenced by multiple genes that, in turn, could affect inflammatory biomarker levels [98, 99]. Based on recent evidence it is possible that the elevated CHI3L1 levels in DM patients are, at least in part, responsible for the endothelial dysfunction and the later micro- and macrovascular complications of DM. The protein expression of CHI3L1 is increased in human smooth muscle cells of atherosclerotic plaques [100] and serum levels of CHI3L1 correlate with arterial wall stiffness – another measure of endothelial dysfunction [101] (fig. 2). In the process of atherosclerotic plaque formation, where smooth muscle cells migrate through the intima in response to exogenous signals, CHI3L1 promotes vascular smooth muscle cell attachment, spreading and migration. This corroborates the idea that CHI3L1 has a role in the process of atherosclerotic plaque formation in response to exogenous signals, and contributes to the process of restenosis and neointima formation. CHI3L1 also modulates vascular endothelial cell morphology by promoting the formation of branching tubules, indicating that CHI3L1 has a role in angiogenesis by stimulating the migration and reorganization of vascular smooth muscle cells [102]. In addition, in atherosclerotic plaques immunohistochemical analysis demonstrated protein expression of CHI3L1 in human smooth muscle cells [103]. The association between CHI3L1 and atherosclerosis has been related to macrophage activation, as also suggested by the demonstration that the inflammatory cytokine TNF-α enhances CHI3L1 expression in macrophages, and confirmed by the finding that TLR2 and TLR4 activation (i.e. by LPS) further increases the release of CHI3L1 in TNF-α-activated THP-1 monocytes [104] (fig. 1). Additionally, in patients with carotid atherosclerosis, CHI3L1 enhances both gelatinolytic and MMP-9 activity in PBMCs and in THP-1 monocytes via p38 mitogen-activated protein kinase (MAPK) activation [104]. Further studies showing the association between CHI3L1 and 'pro-atherogenic' chemokines such as MCP-1 and IL-8 were crucial in understanding the role of CHI3L1 in relation to monocyte/macrophage differentiation, especially in IR and the atherosclerotic process [105, 106]. It is well known that macrophages incorporate oxidized LDL (oxLDL) via the CD36 scavenger receptor pathway, thereby becoming 'foam cells', which are the hallmark of the early fatty streak lesion. Glucose-induced upregulation of CD36 in microvascular smooth muscle cells, followed by increased molecular markers of oxidative stress/damage, as well the increased concentrations of stress response proteins initiates vascular endothelial dysfunction [107, 108]. Elevated levels of CHI3L1 have been detected in the supernatant of macrophages after treatment with oxLDL [109], confirming a role of CHI3L1 in the differentiation of monocytes to 'foam cells' during formation of the atherosclerotic plaque. The elevated serum levels of CHI3L1 in patients with T2DM correlated positively with dyslipidaemia [104]. Previously, it was showed that CHI3L1 expression is highly upregulated in distinct subsets of macrophages in the atherosclerotic plaque that is characterized by the infiltration of monocytes into the sub-endothelial space of the vessel wall and the subsequent lipid accumulation of the activated macrophages [110]. Macrophages infiltrating deeply into the lesion especially show high CHI3L1 expression and, in particular, the highest expression was found in macrophages in the early lesion of atherosclerosis [104]. Monocytes from diabetic patients have significantly higher levels of CD36, CD14 and CD18 expression [111, 112]. CD14 is a key molecule in the innate immune response, where activation of membrane receptors initiates the secretion of pro-inflammatory cytokines and leads to clustering with other receptors involved in atherogenesis, such as CD11b/CD18 and scavenger receptor CD36 [113]. The differentiation and maturation of CD14+ monocytes to CD16+ macrophages is attended by the expression of CHI3L1 [114] (fig. 2). Remarkably, recent ev-

idence indicates a correlation between CHI3L1 and adhesion molecules [115]. In proximity of the CHI3L1 encoding gene, locus 1q32.2 influences the plasma levels of ICAM-1 [116], an adhesion molecule involved in endothelial dysfunction and the development of atherosclerosis. The production of the adhesion molecules VCAM-1, ICAM-1 and E-selectin, which all play a role in endothelial dysfunction preceding atherosclerosis, are stimulated by cytokine mediators such as IL-6 [117]. VCAM-1 and E-selectin also correlate with IR [118]. Patients with T2DM have elevated levels of CRP, IL-6 and the cell adhesion molecules ICAM-1, VCAM-1 and E-selectin [119]. Therefore, elevated levels of CHI3L1 in patients with DM play a greater role in the process of atherosclerosis.

Vascular endothelial growth factor (VEGF) in response to hypoxia is principally regulated by HIF-1α (hypoxia-inducible factor-1α) and plays a key role in angiogenesis and endothelial function [104]. Plasma levels of CHI3L1 correlated positively with sFlt-1/VEGF, suggesting that inhibition of VEGF by circulating sFlt-1 may play a role in the upregulation of CHI3L1 [120]. It is possible that the levels of VEGF may be rate limiting for CHI3L1 regulation, possibly constituting a negative feedback loop. Raised serum CHI3L1 levels have been found in patients with stable CAD, providing prognostic information in these patients [121]. Furthermore, high CHI3L1 levels have been detected during acute myocardial infarction [104] and in patients with carotid plaques, and, in particular, the highest levels were found in patients with symptomatic lesions. Notably, the association between CHI3L1 and symptomatic disease was also found in patients with the most recent symptoms [104]. This observation strongly indicated that CHI3L1 might play a role in plaque stability. Platelets are important mediators of inflammation, at least partly related to their ability to induce monocyte activation [122]. An inflammatory interaction between platelets and monocytes also includes the ability of platelets to promote CHI3L1 expression, as demonstrated by the finding that the β-receptor agonist isoproterenol activated platelets markedly increasing CHI3L1 expression in THP-1 cells [104]. Patients with atherosclerotic disorders, and in particular those with unstable disease, are characterized by enhanced β-adrenergic receptor stimulation and platelet activation [104], which promotes CHI3L1 release within the lesion, further linking CHI3L1 to the unstable patient phenotype. Therefore, CHI3L1 might also be a marker of plaque instability, potentially reflecting macrophage activation and matrix degradation within the atherosclerotic lesion. Overall, the findings regarding tissue distribution and function of CHI3L1 and the concept that CHI3L1 is an inflammatory marker strongly indicate that CHI3L1 plays more than a crucial part in atherosclerotic conditions, such as cardiovascular diseases, and in the pathogenesis of diabetic complications. Future studies should further investigate the potential pro-atherogenic effects of CHI3L1 as well as the utility of CHI3L1 as a risk predictor in patients with atherosclerosis.

CHI3L1 and Diabetic Nephropathy

Diabetic nephropathy is one of the most important complications as a significant cause of end-stage renal disease with high morbidity and mortality. Although clear evidence indicates that the pathogenesis of diabetic nephropathy is multifactorial, inflammation is a key pathophysiological mechanism [123]. The mediators related to the dysfunction and inflammatory pathways are elevated in patients with DM as well as with microvascular complications, and are important in the early stages of diabetic kidney disease. An increasing urinary albumin excretion rate reflects vascular damage in the kidneys as part of systemic endothelial dysfunction [124]. Both micro- and macroalbuminuria are accompanied by increased levels of a variety of markers of endothelial dysfunction [125]. Persistent micro- and macroalbuminuria are well-known predictors of diabetic nephropathy leading to progressive renal insufficiency and end-stage renal disease, and are associated with an increased risk of cardiovascular disease in patients with both type 1 and type 2 diabetes. As a low-molecular-weight protein, CHI3L1 is excreted by the kidney [126], filtered into the early tubular fluid and catabolized in the proximal tubules [127]. Other studies have shown that the urinary excretion of CHI3L1 increases significantly in macroalbuminuric diabetic patients. Nevertheless, it remains unclear whether the cause of enhanced levels of urinary CHI3L1 in macroalbuminuria arises from the tubular damage that causes the reduced tubular reabsorption of filtered CHI3L1 or from increased renal production of CHI3L1, which, in turn, is induced by localized inflammation. Chronic low-grade inflammation is associated with the occurrence and progression of albuminuria [128]. An independent association between high levels of CHI3L1 and albuminuria, which represents an early marker of vascular complications, was detected both in type 1 and type 2 DM patients [81, 126]. These data suggest that CHI3L1 may be considered a potential indicator for risk assessment at least in adults. Since the kidneys excrete CHI3L1, it was not sur-

prising to find a significant correlation between CHI3L1 and the UACR (urinary albumin/creatinine ratio) [84]. The elevated CHI3L1 levels were found to be independently associated with the level of microalbuminuria after adjustment for UACR, age and other significant covariates, and the presence of retinopathy and intermittent claudication. It has been reported that CRP, as a marker of low-grade inflammation, was a determinant of the development of elevated excretion of urinary albumin [129]. However, it was previously demonstrated that both plasma and urine CHI3L1 are not significantly correlated with CRP [84]. In contrast to CRP, which is primarily produced by hepatocytes in response to IL-6 [130], CHI3L1 is produced locally at sites of inflammation [10]. Thus, CHI3L1 has a role as a site-specific inflammatory marker rather than as a systemic inflammatory marker such as CRP. Of note, the CHI3L1 level fulfils prognostic importance in normoalbuminuric patients with preserved kidney function in line with the concept that CHI3L1 acts as an early marker of diabetic nephropathy. Additional evidence demonstrating that CHI3L1 plays an important role in the development of early diabetic nephropathy with conserved eGFR suggests that plasma CHI3L1 measurement might become a useful and non-invasive tool for early incipient diabetic nephropathy as well as for the evaluation of the renal involvement of T2DM patients. Nevertheless, to support the role of CHI3L1 as a pro-inflammatory marker in the early development of diabetic nephropathy, further investigation is needed to determine the correlations with other inflammatory markers, such as TNF-α, interleukins and chemokines.

Diabetic Retinopathy

Diabetic retinopathy (DR) is a microvascular complication of diabetes. Clinically characterized by retinal vascular microaneurysm and blot haemorrhages, DR can be categorized into early non-proliferative DR (mild NPDR), moderate and severe, or pre-proliferative DR and proliferative DR (PDR) [131]. The middle stages include moderate, severe and very severe non-proliferative diabetic retinopathies, generally with hard exudates and maculopathy. In this stage, venous changes, retinal capillary loss, retinal ischaemia, cotton wool or soft exudates, dot, blot spots and extensive intraretinal haemorrhages are evident. The PDR is the disease at the advanced stage characterized by neovascularization, preretinal and vitreous haemorrhages, fibrovascular proliferation and retinal detachments. PDR is one of the major causes of vision loss in subjects with diabetes [131]. Subjects with T1DM have a higher prevalence of PDR than those with T2DM and key risk factors for the development of PDR include hyperglycaemia, diabetes duration and hypertension [131]. Altered epigenetic patterns may contribute to disease development and differential DNA methylation has been found in subjects with T1DM and T2DM compared with non-diabetic controls [132, 133]. Currently, it is supposed that transient peaks of hyperglycaemia might be an independent risk factor for the progression of retinopathy and that hyperglycaemic peaks may cause persistent epigenetic changes in spite of normoglycaemia [134]. Epigenetic modifications may also influence the development of vascular complications in diabetic subjects and recent evidence demonstrates that differential DNA methylation can be associated with DR [135]. Recently, it was found that serum levels of CHI3L1 were elevated in subjects with diabetic retinopathy [20]. Additionally, a decreased DNA methylation of CHI3L1 was observed in a subject affected by PDR, which may contribute to the increased expression of this gene [136]. Previous data showed that there was statistical significance in the levels of plasma concentration of CHI3L1 among two groups of patients with T2DM and different forms of DR [137]. The levels of CHI3L1 in peripheral blood samples have been found to also be elevated in the group with mild NPDR [137]. Moreover, correlation analysis revealed that the outer diameter retinal blood vessels positively correlated with CHI3L1 levels in all zones and in both eyes, and negatively correlated with the number of retinal vessels [137] (fig. 2).

CHI3L1 and Skeletal Fragility

The clinical literature reporting the influence of DM on osteoarthritis (OA) and its therapeutic consequences suggests that DM may increase the risk of the development and severity of OA. Articular cartilage defects cause pain, reduced joint function and significant disability [138]. OA and DM frequently co-exist simply by chance due to their high prevalence and shared risk factors. Nearly half of patients with DM have some form of arthritis. The development of OA may also complicate DM. Increasing evidence indicates that OA adds to the burden of cardiovascular disease, which is higher than average in DM patients [139]. CHI3L1 has been linked to joint injury [140] and significantly elevated levels of CHI3L1 protein have been detected in serum and synovial fluid

from OA patients [25] (fig. 2). In synovial cells CHI3L1 mediates a mitogenic effect through the initiation of MAPK and PI3K signalling pathways by phosphorylation of ERK1/ERK2 (extracellular signal-regulated kinase-1 and -2) and AKT, respectively. Both pathways are required for the cells to complete mitosis and the activation of these pathways stimulates the growth of connective tissue cells [141]. In chondrocytes, CHI3L1 reduces the activation of p38 and SAPK/JNK MAPKs, which counteracts the inflammatory responses to TNF-α and IL-1. This leads to a reduced production of MMPs and IL-8. The modulation of p38 and SAPK/JNK by CHI3L1 is mediated through PI3K [25], and the induction and continued secretion of CHI3L1 requires sustained activation of NF-κB [24]. It has been reported that CHI3L1 interferes with the synthesis of hyaluronan, one of the most widespread and abundant glycosaminoglycan in humans, but no degenerative activity of CHI3L1 against hyaluronan has yet been demonstrated [142]. CHI3L1 is a growth factor for fibroblasts, chondrocytes and human synovial cells [143], and the promotion of growth and proliferation occurs in a dose-dependent manner in a concentration range similar to the effective dose of IGF-1. The regulation of CHI3L1 is scantily evaluated. The secretion of CHI3L1 by human chondrocytes in vitro is not influenced by IGF-1, while transforming growth factor-β reduces the release of CHI3L1 to barely detectable levels [22]. CHI3L1 and IGF-1 work in a synergistic fashion when present in suboptimal concentrations [25]. CHI3L1 was expressed in an osteoarthritic rat cartilage model [140]. These findings suggested that patients with elevated serum levels of CHI3L1 may have a more increased osteolytic activity and a faster progression of the disease. Indeed, silencing CHI3L1 with siRNA resulted in a significant decrease in bone resorption activity and transfection with CHI3L1 siRNA decreased the levels of the pro-differentiation marker MMP9 [16]. The plethora of evidence showing that CHI3L1 stimulates the proliferation of connective tissue cells and modulates expression levels of chemokines and metalloproteases in inflammatory fibroblasts, and that this enhances the chemotaxis of endothelial cells [24], strongly indicates that CHI3L1 plays a crucial role in stromal cells not only in inflammatory conditions. CHI3L1 is expressed in osteophyte and diseased human osteoarthritic cartilage, but not in non-diseased cartilage, and its distribution within the tissue changes as the disease progresses [14]. The number of chondrocytes with a positive staining for both CHI3L1 and CHIT1 was weak or absent in normal cartilage, while the expression for CHI3L1 was very strong in osteoarthritic cartilage with anterior cruciate ligament transection. Their production is closely related to an inflammatory process and pro-inflammatory cytokines [144]. Immunohistochemical analysis confirmed that CHI3L1 staining was found in chondrocytes of osteoarthritic cartilage mainly in the superficial and middle zone of the cartilage rather than the deep zone. There was a tendency for a high number of positive chondrocytes in areas of the femoral condyles with a considerable biomechanical load. CH3L1 presents CBM (carbohydrate-binding motif), followed by the ability to bind carbohydrates, in particular glycosaminoglycan. CHI3L1 could activate pro-inflammatory cytokines through its CBM. This ability might explain the altered levels of these two molecules during a chronic inflammatory process such as OA. Recent articles confirm that the gelatinases influence OA onset and progression, regulating subchondral bone remodelling. In particular, a predominant role of MMP-9 has emerged during last year. Among various MMPs, the total MMP-9 level is positively correlated with the total MMP-13 level in OA [145], and it has been hypothesized that this gelatinase might be involved in the activation of pro-MMP-13 through yet unknown mechanisms. Notably, MMP-13 has long been considered the major enzyme involved in cartilage erosion during OA, thus MMP-9 might play a role, at least co-operatively, in joint degradation. Therefore, it is reasonable that the chitinase may be involved in the resorption of articular cartilage in OA through different pathways. The present finding indicates that CHI3L1 could play an important role in cartilage remodelling/degradation of osteoarthritic joints. CHI3L1 may emerge as a useful marker for OA and tissue degeneration.

Conclusion

CHI3L1 has emerged as a new molecule that may contribute to numerous aspects and phases of diabetes and its complications, including the impaired endothelial dysfunction wound healing and cartilage remodelling/degradation observed in DM (fig. 2). It has become clear that this enzyme may provide valuable information within a clinical setting, potentially acting as a screening tool for high-risk patients and becoming an early predictive diagnostic tool, while informing the treatment decision-making process. Many of the results obtained so far on the involvement of endothelial dysfunction and cartilage remodelling/degradation in diabetic complications have been the result of large screening studies, and have been validated in in vitro cell systems and in in vivo settings.

CHI3L1 accumulating in diabetic tissues could affect biomechanics. Most importantly, we still lack critical knowledge of the pathways involved in CHI3L1 expression. Since CHI3L1 exerts different functions according to the tissues and conditions where it is expressed, we are only seeing a small fraction of the 'big picture'. Maintaining CHI3L1 equilibrium is mandatory to prevent or delay DM complications. The gaining of more understanding into the mechanisms by which CHI3L1 is regulated will provide new tools with which to avoid risk factors eliciting multifactorial diseases such as DM and its complications.

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