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Review

Secreted frizzled-related protein 4 (SFRP4) and fractalkine (CX3CL1) — Potential new biomarkers for β-cell dysfunction and diabetes

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ABSTRACT

The discovery of new risk factors for diabetes is a major challenge for contemporary science. Pathogenesis of type 2 diabetes mellitus (T2DM) is closely related to adipose tissue dysfunction. The aim of this review was to describe recently discovered cytokines: fractalkine (CX3CL1, FKN) and secreted frizzled-related protein 4 (SFRP4) as potential biomarkers of early β cell dysfunction and diabetes. The association of CX3CL1 and SFRP4 with low-grade inflammation in adipose tissue links obesity with disturbances in insulin secretion and impaired glucose metabolism, therefore it indicates new therapeutic and preventive targets in both healthy and diabetic subjects.

Contents

Introduction

Diabetes mellitus and its cardiovascular complications are one of the leading causes of disability and deaths worldwide. According to the International Diabetes Federation (IDF) incidence of diabetes, especially type 2 (T2DM), will rise from 366 million in 2011 to 552 million by 2030, which means that the disease will affect one out of ten adults [1]. In Europe at least 131 billion dollars per year is spent on healthcare due to diabetes [2], which indicates that it is not only an important health, but also a socio-economic problem. Therefore the need for prevention as well as the discovery of new risk prediction factors for diabetes is a major challenge for contemporary laboratory medicine.

Pathogenesis of T2DM is closely linked to adipose tissue dysfunction. Excessive body fat acts as an endocrine organ in which many adverse biochemical mechanisms occur. Cytokines produced by adipocytes such as interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), resistin, retinol binding protein 4 (RBP-4), dipeptidyl peptidase 4 (DPP-4) and adipocyte fatty acid-binding protein (A-FABP) activate inflammation pathways, which decrease the quantity/activity of the insulin-dependent receptors, and affect gene expression and insulin production in human pancreatic islets, leading to insulin resistance and impaired glucose metabolism [3]. By the fact that elevated levels of various chemokines may predict the occurrence of disease even several years before its diagnosis they are considered to be potential risk factors in both apparently healthy, non-diabetic and overweight/obese subjects. Recent studies focused on newly discovered chemokines: fractalkine (CX3CL1, FKN) and secreted frizzled-related protein 4 (SFRP4) as promising biomarkers of early pancreatic β-cell dysfunction, however their diagnostic and clinical utility/relevance is not confirmed yet.

Fractalkine (CX3CL1, FKN)

Fractalkine is the only member of the CX3C chemokine subclass composed of 373 amino acids. It is synthesized as a transmembrane

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molecule consisted of a soluble form — chemokine domain and the extracellular mucin-like stalk and the membrane-bound form (Fig. 1). The soluble CX3CL1 is generated by disintegrin-like metalloproteinases (ADAM) 10 and 17/TACE and has the chemoattractive activity for monocytes, natural killer (NK) cells, and T cells [4]. Membrane-bound form is produced in endothelial and epithelial cells, vascular smooth muscle cells, keratinocytes, dendritic cells, and neurons after stimulation by pro-inflammatory factors, such as TNF-α, interferon γ (IFN-γ), and IL-1, and supports integrin-independent leukocyte adhesion [5]. The presence of mRNA for FKN has been showed in various organs such as heart, kidneys, liver, adrenal gland and brain. The activity of CX3CL1 is related to its receptor called CX3CR1. This receptor occurs on the surface of monocytes, macrophages, NK cells, some T cells, neutrophils, mast cells, platelets, smooth muscle cells, and dendritic and microglia cells [4].

The discovery of fractalkine changed the existing opinions upon cell adhesion and migration through the endothelium. According to the classical pathway migration of leukocytes is dependent on the selectin-mediated interactions between leukocytes and the endothelium and activation of integrins on leukocytes by chemokines presented on glycosaminoglycans. Therefore it was claimed that all chemokines are produced as soluble molecules associated with proteoglycans on the cell surface and tissue matrix. In contrast, membrane-bound form of FKN has a chemokine domain on the top of the mucin-like stalk, which acts as an adhesion molecule and is involved in all stages of the migration, while the soluble form shows strong chemotactic effect [6]. Leukocytes with CX3CR1 receptor connect selectively with a chemokine domain presented on endothelial cells which triggers rapid binding. Interaction between CX3CL1 and its receptor additionally can increase expression of integrins, intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) in leukocytes, which may result in stronger adhesion. Expression of fractalkine during the inflammation can also attract and activate NK cells, which are responsible for cytotoxic effect and cytolysis, therefore its contribution to inflammation-dependent conditions seems to be very important [5].

Several studies confirmed the role of fractalkine in the pathogenesis of many human diseases, such as atherosclerosis and cardiovascular disease, rheumatoid arthritis, HIV and HCV infections and cancer in which activity of inflammatory factors is significant [7–10]. Type 2 diabetes is strictly associated with obesity and related to adipose tissue inflammation. In this process a recruitment of monocytes to fatty tissue plays a key role and initiates the first local production of cytokines and then leads to systemic inflammation and insulin resistance. FKN with its dual properties in the mechanism of leukocyte chemotaxis and adhesion might be a relevant pathogenetic factor in early adipocyte dysfunction and T2DM [11], although the data in this area are scarce. Study by Shah et al. [12] clearly confirmed that CX3CL1 is expressed and secreted by human adipocytes and stromal vascular cells, hence it can be considered as adipocytokine. This well-designed study was performed based on in vivo endotoxemia and adipose tissue biopsies in lean and obese subjects, in vitro study of primary human adipocytes and monocytes and case–control study performed in individuals with and without T2DM. Moderate dose (3 ng/kg) of endotoxin (standard lipopolysaccharide, LPS) increased significantly both adipose and blood FKN (33-fold, $p < 0.001$ and over 40-fold, $p = 0.006$ after 4 h, respectively). Subcutaneous adipose tissue levels of CX3CL1 were higher in obese compared with lean subjects (mean 0.420 vs. 0.228 ng/mL; $p = 0.04$) and in obese individuals, these levels were higher in visceral than in subcutaneous adipose tissue (mean 0.736 vs. 0.420 ng/mL; $p = 0.01$). Stimulation of CX3CL1 mRNA expression and protein secretion from adipocytes in vitro by LPS, TNF-α and IFN-γ was observed. Moreover, the use of CX3CL1 blocking antibody reduced monocyte adhesion to adipocytes by almost 50% ($p < 0.001$). Plasma FKN was significantly lower in non-diabetic subjects compared to T2DM patients (mean 0.422 vs. 0.506 ng/mL; $p < 0.0001$). A significant 2.77 odds ratio for diabetes for a 1 SD (0.21 ng/mL) increase in CX3CL1 concentration after adjusting for gender, BMI, ethnicity and other metabolic risk factors was indicated.

The effect of controlled low-dose endotoxemia on fractalkine expression in human adipocytes in vitro was also observed by Mehta et al. [13]. In this study CX3CL1 mRNA increased 15-fold ($p < 0.001$) 4 h after 0.6 ng/kg LPS administration and it was the largest increase compared to the other cytokines (IL-6, TNF-α and MCP-1). Analysis of the impact of endotoxemia on impaired insulin activity showed 32% increase in HOMA-IR ($p < 0.01$) and 21% decrease in insulin sensitivity ($p < 0.05$) in LPS-treated subjects compared to placebo. Presented results broadly highlight the influence of adipose tissue inflammation including fractalkine-mediated pathway on T2DM development,

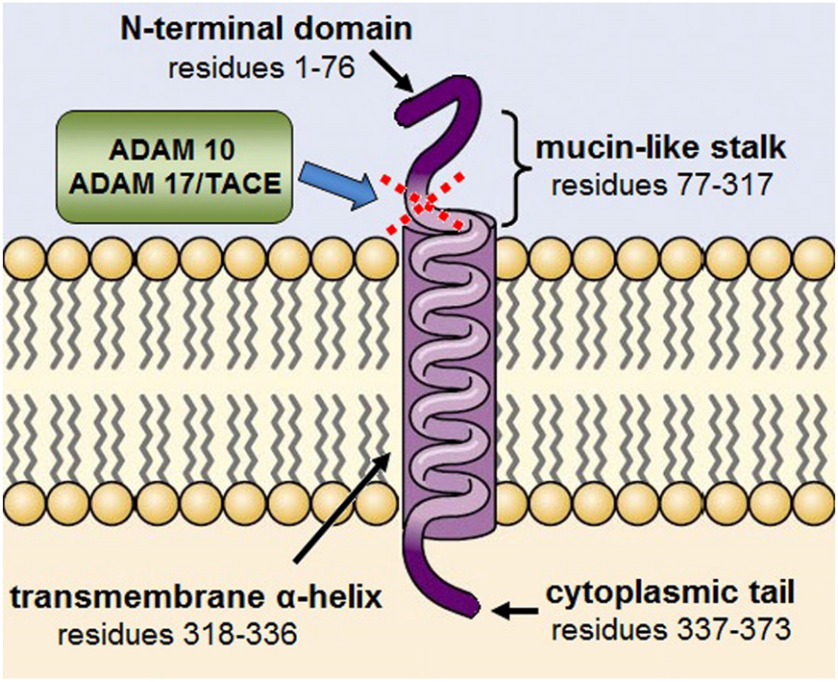

Fig. 1. Fractalkine (CX3CL1) structure.