The roles of annexins in vascular endothelium dysfunction accompanying diabetes mellitus type 2

ABSTRACT

Impairment in cellular transport, distribution and storage of cholesterol accompanies insulin resistance and diabetes mellitus type 2 as well as other diseases such as obesity, atherosclerosis, and non-alcoholic fatty liver disease. Diabetes mellitus type 2 is a metabolic disorder that is characterized by hyperglycemia in the context of insulin resistance and relative lack of insulin. Type 2 diabetes makes up about 90% of cases of diabetes. Several therapeutic strategies are today being considered to target diabetes mellitus type 2, and the accompanying endothelial dysfunction, but none as yet has proved satisfactory. Accumulating data suggest that annexins, as cholesterol binding proteins that participate in intracellular transport and storage of cholesterol and in the organization of plasma membrane, may participate in development and sustenance of diabetes mellitus type 2 and may serve as predictive markers of this disease.

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INTRODUCTION

It is thought that reduced sensitivity of cells to insulin (the insulin resistance syndrome -anomalous response to insulin-mediated glucose disposal) and development of type 2 diabetes (T2D) is related to obesity and is particularly dangerous for people who are genetically predisposed to it. Such patients frequently display elevated blood pressure and hyperlipidemia. Substantial clinical and experimental evidence suggests that both diabetes and insulin resistance cause a combination of endothelial dysfunctions [1-3]. It is postulated that a synergistic interaction may exist in which endothelial dysfunction contributes to insulin resistance and T2D and *vice versa* (Fig. 1).
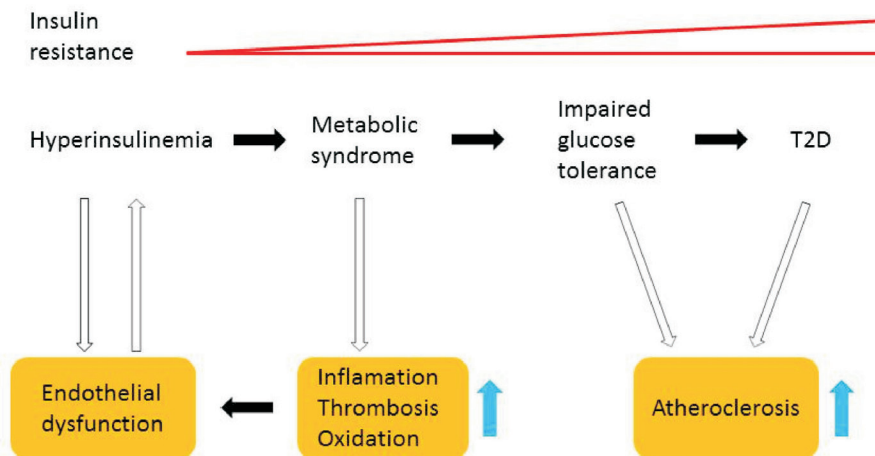

Figure 1. Progression of endothelial dysfunction in relation to the progression of insulin resistance (adapted from [65]).

Moreover, a growing number of evidence suggests that reduced sensitivity of cells to insulin is related to the level of adiponectin, a protein hormone that modulates a number of metabolic processes, including glucose metabolism and fatty acid oxidation. Adiponectin is secreted from the adipose tissue to the bloodstream and plays a role in insulin resistance [4]. Low adiponectin may contribute to disturbed reverse cholesterol transport (RCT) in T2D and development of endothelial dysfunction [5]. Moreover, it has been reported that in monocytes adiponectin may reduce expression of annexin A6 (AnxA6), that in turn inhibits cholesterol efflux. Furthermore, the level of AnxA6 positively correlates with body mass index and negatively with the level of adiponectin in the blood; AnxA6 is abundant in monocytes from obese and type 2 diabetes individuals. It has been demonstrated that adiponectin reduced AnxA6 and enhanced

cholesterol efflux in monocytes [6]. It has to be underlined that several therapeutic strategies are today being considered to target diabetes mellitus type 2 and the accompanying endothelial dysfunction but none proved satisfactory so far. In addition, the mechanism of abnormal cholesterol metabolism is not well understood. A locus on chromosome 9p13-q21 containing the gene *ANXA1* encoding annexin A1, a protein suggested to participate in insulin secretion and propagation of insulin signal, has been identified [7].

On the basis of observations mentioned above, in this article I propose that some annexins, as cholesterol binding proteins that participate in intracellular transport and storage of cholesterol and in organization of plasma membranes in endothelial cells, may participate in development of T2D. and may serve as predictive markers of this disease.

IMPAIRED EFFLUX OF CHOLESTEROL IN ENDOTHELIAL DYSFUNCTION ACCOMPANYING DIABETES MELLITUS TYPE 2 AND ATHEROSCLEROSIS

Type 2 diabetes is a metabolic disorder characterized by hyperglycemia and relative lack of insulin. The classic symptoms are excess thirst, frequent urination, and constant hunger. T2D accounts for about 90% of cases of diabetes, with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes. Obesity is thought to be the primary cause of type 2 diabetes in people who are genetically predisposed to the disease. Fraction of type 2 diabetes mellitus cases associated with physical inactivity ranges from 3% to 40% [8,9]. The incidence rates of T2D have increased markedly since 1960 in parallel with obesity. As of 2010 there were approximately 285 million people diagnosed with the disease compared to around 30 million in 1985. Long-term complications from high blood sugar can include heart disease, strokes, diabetic retinopathy, kidney failure, and poor blood flow in the limbs. Most cases of diabetes involve many genes, each being a small contributor to an increased probability of T2D development . As of 2011, more than 36 genes that contribute to the risk of T2D have been identified. However, all these genes still account for only 10% of the total heritable component of the disease [10,11].

In the light of the results of recent experiments it appears that recovery of physiological response of endothelial cells to insulin at an early stage of development of insulin resistance could have important therapeutic impact.

The principal causes of morbidity and mortality in T2D are coronary artery, cerebrovascular and peripheral vascular diseases. The accelerated macrovascular disease in type 2 diabetes mellitus is due partly to the increased incidence of cardiovascular risk factors, such as hypertension, obesity and dyslipidemia. The endothelium is a major organ exposed to cardiovascular risk factors, such as hypercholesterolemia, hypertension, inflammation, ageing, postmenopausal status, and smoking. Changes in endothelium function may lead to the coronary artery circulation being unable to cope with the increased metabolism of myocardial muscle independently of a reduced coronary artery diameter [12].

Endothelial dysfunction (vascular endothelium being the most studied target) can arise due to insulin resistance, dys-

lipidemia or hypertension that accompany T2D [13]. Vascular endothelium has important regulatory functions in the cardiovascular system and a pivotal role in the maintenance of vascular health and metabolic homeostasis. It has long been recognized that endothelial dysfunction participates in the pathogenesis of atherosclerosis from early preclinical lesions to advanced thrombotic complications. In addition, endothelial dysfunction has been recently implicated in the development of insulin resistance and T2D [14].

In T2D, the structure and composition of high-density lipoprotein (HDL) is altered compared with HDL from normal subjects. HDL from diabetic subjects becomes largely dysfunctional since it has reduced anti-oxidative activity, lower ability to stimulate endothelial cell production of nitric oxide and endothelium-dependent vasomotion, It also fails to promote endothelial progenitor cell-mediated endothelial repair. In addition, HDL from diabetic patients promotes endothelial cell proliferation, migration and adhesion to the matrix [15]. Finally, deregulation of the cellular transport of cholesterol that accompanies endothelial dysfunction in T2D, affects the reverse cholesterol transport.

RCT is a multi-step process resulting in the net movement of cholesterol from peripheral tissues back to the liver via the plasma. This process is regulated by miRNA particles that control expression of most of the genes associated with HDL metabolism, including genes encoding the ATP transporters, ABCA1 and ABCG1, and the scavenger receptor SRB1 [16]. RCT is thought to be one of the primary pathways that protect against atherosclerosis, which is the major cause of cardiovascular diseases and the leading cause of death in industrialized countries. The first and rate-limiting step of RCT is ATP-binding cassette transporter A1 (ABCA1) and ABCG1-mediated cholesterol efflux from the cells. Recently, caveolin-1, a scaffolding protein that organizes and concentrates certain signaling molecules and receptors within caveolae membranes, has been shown to regulate ABCA1 and ABCG1-mediated cholesterol efflux probably via interacting with the transporters [17,18]. Phosphatidylcholine-specific phospholipase C (PC-PLC) is a key factor in apoptosis and autophagy of vascular endothelial cells. It is involved in atherosclerosis in apolipoprotein E$^{-/-}$ (apoE$^{-/-}$) mice. Among important regulatory factors of cholesterol metabolism is also a member of the annexin family of proteins that possesses GTPase activity, namely AnxA7 [19].

ANNEXINS AND ENDOTHELIUM

Annexins belong to a family of membrane interacting proteins, widely distributed in vertebrates [20-24]. Their involvement in the endosomal transport is due to the ability of annexins to bind cellular constituents such as membrane phospholipids and intracellular proteins in a calcium dependent manner. Furthermore, annexins, through endosomal transport of certain receptors and specific cargo, may regulate various processes involved in signal transduction. After activation by a signaling molecule cell surface receptors are internalized by endocytosis and transduce the signal further downstream. The most optimal conditions for signal transduction are provided by compartment specific membrane platforms carrying appropriate/specialized signal transducing complexes. Examples

are the late endosomal platforms containing EGFR and annexins A1 (AnxA1), A2 (AnxA2), A6 and A8 (AnxA8) [25-29].

Annexins, due to their specialized structure and specific localization in the cell, may modulate signal transduction either directly, by interacting with EGF receptor (EGFR), or indirectly by interacting with EGF pathway regulators and effectors, or by participating in the formation and stabilization of cholesterol enriched signal transduction platforms or by participating in EGFR transport and degradation [30-36].

Recently, it has been shown that redox-sensitive endothelial dysfunction, early ischemia/reperfusion, and localized coagulation accompanying transplantation of islets are characterized by the release of microparticles (plasma membrane procoagulant vesicles, surrogate markers of stress and cellular effectors) from endothelium in which EPCR/PAR-1 and ANXA1/FPR2-dependent pathways are involved. Furthermore, these pathways are suggested to be involved in preventing insulin release from islets in response to glucose upon stress [37]. A novel anti-inflammatory mechanism of high density lipoprotein action through up-regulation of AnxA1 has been described in vascular endothelial cells. High density lipoproteins increased endothelial AnxA1 and prevented a decrease in AnxA1 in TNF-α-activated endothelial cells in vitro. HDL-induced AnxA1 inhibited cell surface VCAM-1, ICAM-1 and E-selectin, and secretion of MCP-1, IL-8, VCAM-1 and E-selectin, thereby inhibiting monocyte adhesion to endothelium [38]. Leukocyte recruitment to activated endothelial cells *via* cell surface delivery of CD63 was described to be regulated also by AnxA8 [39]. The expression of AnxA1 in vascular endothelium was affected by oxidative stress [40].

Stressful conditions, such as mechanical stress, may also evoke endothelium dysfunction in which Ca^{2+}-dependent plasma membrane repair mechanism is switched on [41,42]. This mechanism involves annexin A2 (AnxA2) as well as AnxA1 and AnxA6 which are rapidly recruited to the sites of plasma membrane injury in endothelial cells [43].

Another interesting mechanism related to survival of human umbilical vein endothelial cells (HUVECs) was solved by Ma *et al*. [44]. The authors have shown that expression of Homeobox containing 1 (HMBOX1), which is essential for the survival of HUVECs, depends on the GTPase activity of annexin A7 (AnxA7). When this activity was inhibited by 6-amino-2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine this promoted HMBOX1 translation by increased expression of TGFB2 overlapping transcript 1 (TGFB2-OT1) and as a consequence expression of La-related protein 1 (LARP1) [44]. AnxA7 was found to be also involved in in regulating vascular endothelial cell autophagy by interaction with T-cell intracellular antigen-1 (TIA1) [45].

ANNEXINS AND CHOLESTEROL

ANNEXINS AND THE VESICULAR
TRANSPORT OF CHOLESTEROL

Observations briefly reviewed in the former paragraphs strongly suggest that annexins may affect distribution and activity of various important signaling proteins in a calcium- and cholesterol-dependent manner [46-51].

Cholesterol regulates association of several important signal transduction molecules, including SNAP receptors (t-SNAREs), with the plasma membrane. It has been recently demonstrated that high levels of AnxA6 induce accumulation of cholesterol in late endosomes, thereby reducing cholesterol in the Golgi and plasma membrane. This leads to an impaired supply of cholesterol needed for cytosolic phospholipase A_2 ($cPLA_2$) to drive Golgi vesiculation and caveolin transport to the cell surface. By using AnxA6-overexpressing cells as a model for cellular cholesterol imbalance, the investigators observed impaired cholesterol egress from late endosomes and diminution of Golgi cholesterol, which correlated with the sequestration of t-SNAREs. Similar phenomenon was observed when accumulation of cholesterol in late endosomes and inhibition of $cPLA_2$ were evoked pharmacologically. Ectopic expression of Niemann-Pick C1 (NPC1) or exogenous cholesterol restored the location of t-SNAREs within the plasma membrane. In conclusion, it has been stated that AnxA6-mediated mislocalization of t-SNAREs correlates with reduced secretion of cargo via the t-SNAREs-dependent constitutive exocytic pathway [52]. Inhibition of cholesterol export from late endosomes causes cellular cholesterol imbalance, including cholesterol depletion in the trans-Golgi network (TGN) [53].

It has been shown that AnxA6 may affect influenza A virus life cycle by shifting cellular cholesterol pools in a Ca^{2+}-dependent manner. Elevated levels of cellular AnxA6, which decrease plasma membrane and increase late endosomal cholesterol levels, resulted in impairment of virus replication and propagation, whereas RNA interference-mediated AnxA6 ablation increased viral progeny titers. Pharmacological accumulation of late endosomal cholesterol also diminished virus propagation. Decreased virus replication caused by upregulated AnxA6 expression could be restored either by exogenous replenishment of host cell cholesterol or by ectopic expression of the late endosomal cholesterol transporter Niemann-Pick C1 (NPC1) [54].

It has been also reported that loss of AnxA8 in human umbilical vein endothelial cells strongly decreased cell surface presentation of CD63 and P-selectin, with a concomitant reduction in leukocyte rolling and adhesion [39].

CHOLESTEROL REGULATES ANNEXIN
DISTRIBUTION AND FUNCTION IN THE CELL

Lipid rafts, cholesterol-enriched membrane microdomains, may play a role as platforms for signal transduction and metabolic pathways in T2D [30,33,34]. Many members of the annexin family have been localized in membrane microdomains resembling rafts [30]. This was observed for AnxA2 and its heterotetramer with the S100A10 protein ($AnxA2_2S100A10_2$) [55-57]; the latter is most probably implicated in microdomain-supported exocytosis of neurotransmitters and promotes the lateral association of glycosphingolipid- and cholesterol-enriched lipid microdomains into larger assemblies. The association of AnxA2 with lipid rafts was found to be influenced not only by intracellular $[Ca^{2+}]$ but also by N-terminal phosphorylation at Tyr23 residue. In addition it has been observed that the binding of AnxA2 to the lipid rafts is followed by the transport of proteins along the endocytic pathway [33,58].

The cholesterol-enriched microdomains described above may serve as platforms for spatial and temporal organization of signal transduction pathways, creating a link between different extracellular stimuli and distinct cellular responses. A classic example are the multiple signaling pathways activated by protein kinase C (PKC) isoforms. It has been reported that several annexins, including AnxA1, AnxA2, AnxA5 and AnxA6, display specific and distinct abilities to interact and promote membrane targeting of different PKC isozymes. Together with the ability of annexins to create specific membrane microenvironments, this is likely to enable PKCs to phosphorylate certain substrates and regulate their downstream effector pathways at specific cellular sites [58].

Among the isoforms of PKC, PKCα can phosphorylate EGFR at threonine 654 (Thr654) to inhibit EGFR tyrosine phosphorylation (pY-EGFR) and the associated activation of downstream effectors. It has been shown that ectopic expression of AnxA6 strongly reduces pY-EGFR levels while augmenting Thr654 phosphorylation in EGFR-epidermal (A431), head and neck and breast cancer cell lines. Reduced EGFR activation in AnxA6 expressing A431 cells is associated with reduced EGFR internalization and degradation. This strongly suggests that annexins are implicated in the vesicular transport and various signal transducing pathways [27,59].

It must be stressed that cell signaling and endocytosis are intimately linked in eukaryotic cells [60]. Furthermore, the endocytic compartment is thought to be a functional platform for controlling important cellular processes [61]. Signaling receptors at the cell surface enter the endocytic pathway and continue to activate downstream effectors in endosomal compartments. Members of the annexin protein family, in particular AnxA1, AnxA2, and AnxA6, appear to target their interaction partners to specific membrane microdomains thereby contributing to the formation of compartment-specific signaling platforms along the endocytic pathway [62].

CONCLUDING REMARKS

Experimental evidence along with the analysis of primary structures favors the idea that some annexins, especially AnxA2, AnxA6 and AnxA13 resemble genuine cholesterol-interacting proteins, and that intracellular localization and membrane binding of annexins at low pH is determined by cholesterol [32,63,64]. Furthermore, experimental data suggest that certain functions of annexins may be regulated by cholesterol and, last but not least, that annexins may participate in cholesterol traffic and storage. Factors were identified that play a role in regulation of annexin-membrane interactions, including calcium, pH and membrane lipid composition. A growing number of evidence, coming mostly from in vitro experiments, suggests that cholesterol may affect the affinity constants of annexins binding to artificial lipid membranes such as liposomes of various chemical composition or solid supported lipid membranes. Sequence alignment of different human annexins revealed domains

that are most probably crucial for the annexin-membrane binding [30].

The results of preliminary in vitro experiments performed in our Laboratory have revealed that 48 h incubation of the endothelial hybrid cell line EA.hy 926 (established by fusing a human umbilical vein endothelial cell with a human carcinoma cell) with palmitate significantly reduces cell response to insulin, as visualized by a lower level of kinase Akt phosphorylation (dr Dorota Dymkowska, Nencki Institute of Experimental Biology, Warsaw, personal communication). Furthermore, preliminary results shown in figure 2 [65-67]
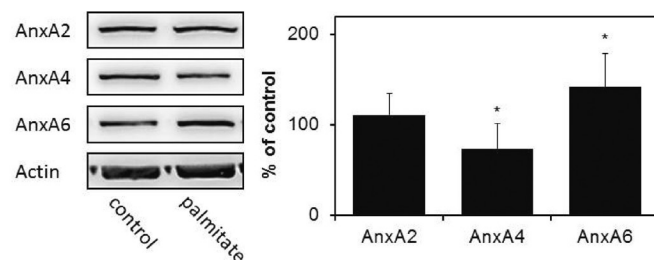
Figure 2. Changes in expression of annexins in human epithelial EA.hy926 cells in culture in the presence of 100 μM palmitate. The obtained results are shown as means ± S.D. (the right panel; n=4, *p<0.05 *versus* control cells not treated with palmitate) (dr Marcin Woś, Nencki Institute of Experimental Biology, unpublished results).

suggest that palmitate treatment alters the expression of annexin encoding genes in human epithelial EA.hy926. It is worth to remember that palmitate was recently reported to increase inflammation and enhance the ability of epithelial cells to bind monocytes *in vitro*, therefore, it could be an important factor influencing cardiovascular health [68]. On the basis of our preliminary results and the aforementioned literature data we hypothesize that palmitate-induced insulin resistance of vascular endothelium may affect annexin-dependent cholesterol metabolism and finally accelerate endothelial cell injury.

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Udział aneksyn w nieprawidłowym funkcjonowaniu komórek śródbłonka naczyniowego towarzyszącemu cukrzycy typu 2

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Słowa kluczowe: aneksyny, cholesterol, nieprawidłowe funkcjonowanie nabłonka naczyń krwionośnych, mitochondria, organizacja błon mitochondrialnych

STRESZCZENIE

Zaburzenia wewnątrzkomórkowego transportu, rozmieszczenia i magazynowania cholesterolu, towarzyszą rozwojowi insulinooporności i cukrzycy typu 2, a także innych chorób cywilizacyjnych, takich jak otyłość, miażdżyca i choroby wątroby. Cukrzyca typu 2 jest chorobą metaboliczną, dla której charakterystyczna jest hiperglikemia (przecukrzenie), co jest związane z rozwojem insulinooporności i zaburzeniami zawartości insuliny. Stanowi 90% wszystkich przypadków cukrzycy. Rozwijane jest szereg strategii terapeutycznych w celu leczenia choroby i towarzyszącego jej nieprawidłowego funkcjonowania śródbłonka naczyń krwionośnych, ale żadna z nich nie jest w pełni satysfakcjonująca. Zgromadzone dane doświadczalne dotyczące aneksyn jako białek wiążących cholesterol i uczestniczących w transporcie i gromadzeniu tego lipidu oraz w organizacji błony plazmatycznej, wydają ię wskazywać na udział tych białek także w rozwoju i utrzymywaniu cukrzycy typu 2. Rozważa się również możliwość zastosowania aneksyn w przyszłości stosowane jako znaczników cukrzycy typu 2.