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LEUKOCYTES IN TYPE 1 DIABETES MELLITUS: THE CHANGES THEY UNDERGO AND INDUCE

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As leukocytes represent cellular and humoral immunity at the same time, they are a vital part of every immune process. This also stands for autoimmune processes and disorders, such as diabetes, specifically type 1 diabetes mellitus. Diabetes mellitus is one of the most widespread autoimmune diseases. Development of type 1 diabetes mellitus is mediated through complicated mechanisms of intercellular communication where leukocytes function as the key element, being both effectors and regulators. However, the immunocompetent cells are also affected by diabetic alterations, powered by chronic hyperglycemia. For example, the products of non-enzymatic interaction of glucose or other reducing sugars with either proteins or lipids, called advanced glycation end products, are associated with the development of long-term negative changes in diabetes. By binding to the receptors for advanced glycation end-products, they trigger the signaling pathways involved in expression of pro-inflammatory genes, which results in diabetic complications. As long as diabetes mellitus remains a global healthcare issue and several details of its pathogenesis are still to be discovered, it is important to analyze and investigate the peculiarities of alterations in leukocytes under type 1 diabetes mellitus, particularly the ones caused by advanced glycation end-products and their receptors.

Keywords: type 1 diabetes mellitus, leukocytes, advanced glycation end-products, receptors for advanced glycation end-products

INTRODUCTION

Leukocytes are important effector cells of immune system and immune regulators that recognize and remove foreign and damaged cells, antigens and thus maintain tissue homeostasis. Monocytes/macrophages, neutrophils and lymphocytes have been shown to both regulate the development and influence the progression of diabetes mellitus (DM) (Bajpai, & Tilley, 2018).

Type 1 DM (T1DM) is a multifactorial disease; however, the main cause of the T1DM pathogenesis is the impairment of auto tolerance mechanism of the organism, which leads to an autoimmune response. For type 1 DM, recognition of proteins of insulin-producing pancreatic β-cells as autoantigens by autoreactive $CD4^+$ and $CD8^+$-cells and antibodies is characteristic. This, in turn, leads to islet cells destruction, insulin deficiency, chronic hyperglycemia, and, respectively, a clinical manifestation of the disease with the risk of microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (peripheral artery disease, coronary artery diseases, congestive heart failure, myocardial infarction, stroke) complications.

Hyperglycemia causes intensified non-enzymatic glycosylation of proteins and lipids and the subsequent generation of reactive compounds and accumulation of AGEs (Basta, 2004). It is known that AGEs are able to form intra- and extracellular crosslinks with different macromolecules (proteins and polyunsaturated fatty acyl residues of structural lipids), which results in their structural and functional alterations (Goldin, Beckman, Schmidt, & Creager, 2006), reduced fluidity of membranes, and, in particular, changes in the migration of leukocytes that further leads to the development of diabetic complications. In addition, AGEs are an important diagnostic biomarker that allows for estimating the influence of applied treatment on disease progression. Prevented generation or reduction of AGEs level has therapeutic potential to slow progression of diabetic complications (Zhang *et al*., 2016).

The impact of AGEs is determined by the interaction with cell surface receptors – RAGEs, which activates various signaling pathways in leukocytes, particularly NF-κB, and stimulation of proinflammatory factor release. All of these changes provoke imbalance in the functional activity of leukocytes contributing to the development of diabetic complications and concomitant comorbidities. A possible mechanism of protection against the detrimental effects of activation of these signaling pathways is to generate circulating soluble forms of RAGEs that prevent intracellular proinflammatory signal transduction by binding AGEs (Cao, Hou, & Nie, 2014).

1. Type 1 diabetes mellitus: etiology and molecular mechanism of development. Diabetes mellitus is a chronic, metabolic disorder, characterized by elevated blood glucose levels and impairment of protein, carbohydrate, and lipid metabolism along with organ and tissue damage. There are three main types of DM: type 1 (insulin-dependent), type 2 (insulin-independent) and gestational diabetes. Other specific types of DM are quite rare (~6 % of all cases) and occur due to chronic inflammation of the pancreas (pancreatitis), diseases of other endocrine glands (thyroid, hypophysis, adrenal glands), effect of certain drugs, etc. (Punthakee, Goldenberg, & Katz, 2018). Diabetes mellitus is manifested when fasting glucose level in blood exceeds 7.7 mmol/L, which is caused by insulin deficiency or impaired ability of cells to respond to insulin (Dilworth, Facey, & Omoruyi, 2021).

Type 1 DM accounts for nearly 10 % of cases of diabetes around the world. There are two subcategories of type 1 diabetes: autoimmune type 1 (ADM) and idiopathic type 1 diabetes (IDM). The latter one is characterized by a decrease in β-cell functional activity with the symptoms of insulinopenia, ketosis, and ketoacidosis. At the same time, autoimmune β-cell destruction markers are absent (American Diabetes Association, 2014). Autoimmune type 1 diabetes associates with hyperglycemia, which results from an absolute insulin deficiency, and occurs because of autoimmune destruction of pancreatic β-cells due to a T-cell-mediated inflammatory response and a humoral (B-cell) response (Katsarou *et al*., 2017; Kawasaki, 2014; Kharroubi, 2015).

The destruction of β-cells can be genetically predetermined or related to the influence of environmental factors (American Diabetes Association, 2014). Exogenous factors are potential triggers for immune-mediated β-cell destruction. These factors include β-cells tropic viruses, toxins, exogenous and endogenous cytotoxic compounds (Katsarou *et al*., 2017; Paschou, Papadopoulou-Marketou, Chrousos, & Kanaka-Gantenbein, 2018). An exposure to viruses or chemical agents activates cellular and humoral immunity, dendritic cells, macrophages and lymphocytes infiltrate the pancreas, an inflammation of pancreatic islets (insulitis) develops, and autoantigens are expressed on the surface of β-cells (**Fig. 1**). Recognized autoantigens include such molecules as glutamic acid decarboxylase form (GAD65), proinsulin, insulin B-chain, insulinoma-associated protein 2 (IA2), islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP), chaperone Hsp60, non-specific islet cell antigen (ICA), and islet cell antigen 69 (ICA69) (Marca, Gianchecchi, & Fierabracci, 2018; Xie, Chang, & Zhou, 2014). Either proinsulin or insulin is supposed to be the main antigen involved in those processes (Xie *et al*., 2014).

Antigen presenting cells (APC: dendritic cells, macrophages, B lymphocytes) engulf autoantigens and present them to naïve T-cells together with class II molecules of the major histocompatibility complex (MHC), and thus induce the production of autoreactive $CD4^+$-cells (**Fig. 1**) (Marca *et al*., 2018; Xie *et al*., 2014). These activated $CD4^+$ T-cells synthesize cytokines that activate cytotoxic β-cell specific $CD8^+$ T-cells. Meanwhile, APC release interleukine-12 (IL-12) which activates T-helpers (Th1) causing defections in the immune balance between the effector cells of the adaptive and innate immunity and the regulatory cells. During autoimmune processes, Th1 cells activate B-cells to enhance the generation of antibodies, which, in turn, participate in a further inflammation and destruction of the pancreas (Marca *et al*., 2018). Th1 cells produce IL-2 and interferon-γ (IFN-γ). These compounds activate Pre Cytotoxic T-cells (Pre CTL) and macrophages, and thus transform them into cytotoxic T-cells (CTL). Macrophages excrete inflammatory mediators, toxic for β-cells: IL-1β, tumor necrosis factor-α (TNF-α), IFN-γ, and also free radicals (**Fig. 1**).

An elevated Fas-ligand and TNF-α expression leads to the activation of a receptor-mediated mechanism of apoptotic β-cell death (Fas/FasL) (Paschou *et al*., 2018). At the same time, $CD8^+$-cytotoxic T-cells recognize antigens exposed on β-cells, combined with class I MHC molecules and release granzyme and perforin (cytolysin) that are the cause of necrotic destruction of the cells. Thus, synergistic action of APC, lymphocytes and cytokines is aimed at β-cell destruction, which results in the progression of autoimmune type 1 diabetes (**Fig. 1**) (Cnop *et al*., 2005; Mallone, & Brezar, 2011; Yoon, & Jun, 2005).

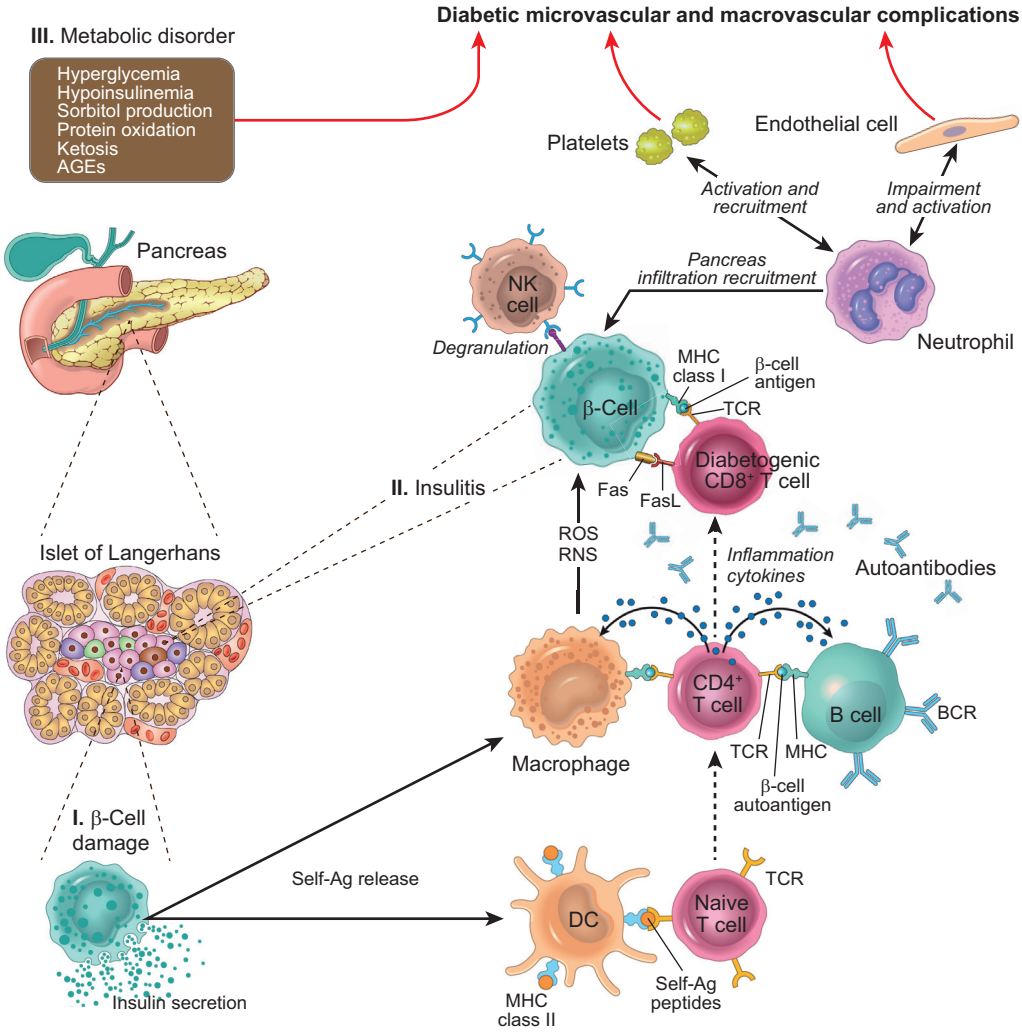

Fig. 1. Type 1 DM immunopathogenesis. Pancreatic islets contain insulin-producing β-cells. Damage and death of β-cells lead to a release of autoantigens (Self-Ag) and activation of antigen-presenting cells (APC: macrophages, DC – dendritic cells, B-cells). APC present β-cellular peptides to $CD4^+$-cells that are responsible for activation of autoreactive $CD8^+$ T-cells. Diabetogenic $CD4^+$ and $CD8^+$ T-cells infiltrate islets of Langerhans and form an inflammatory environment in which β-cells are destroyed. Activated $CD8^+$-cells lyse β-cells carrying autoantigens on their surface together with the main histocompatibility complex (MHC) molecules class I in pancreatic islets. T-Cell receptors (TCR) of diabetogenic $CD8^+$ T-cell recognize β-cell antigen bound to MHC class I on the surface of β-cells, creating an immunological synapsis, which enhances the Fas ligand (FasL) expression inducing β-cell apoptosis. Destruction of β-cells is intensified by proinflammatory cytokines and reactive oxygen and nitrogen species (ROS/RNS) originated from innate immunity cells. In pancreatic islets, activated T-cells stimulate the production of antibodies complementary to β-cellular proteins by B-cells, which is considered to be a biomarker of the autoimmune response development in type 1 DM; BCR – B-cell receptor; Fas – cell surface death receptor; NK cell – Natural Killer cell

Other types of leukocytes also determine an onset and progression of type 1 DM, such as neutrophilic granulocytes and NK cells (**Fig. 1**). A physiological death of β-cells is considered to be an important trigger of the disease development, which activates and induces a migration of competent immune cells (especially neutrophils) to the inflamed areas of the pancreas. The cytotoxic substances produced and secreted by neutrophils, e.g. degranulation products, cytokines, ROS/RNS, extracellular traps, induce the destruction of β-cells of pancreatic islets. Moreover, neutrophils are able to initiate the type 1 DM development by means of a cell-cell interaction with other immune and non-immune cells (**Fig. 1**). In response to the stimulating influence of immunoglobulin G secreted by B-cells, neutrophils release cathelicidin-related antimicrobial peptide (CRAMP). Immunoglobulin G and CRAMP recruit dendritic cells, which is followed by an increased production of IFN-γ. Crosstalk between these immune cells induces a diabetogenic T-cell response resulting in type 1 diabetes initiation. In addition, an interaction between neutrophils and other non-immune cells (platelets and endothelial cells of blood vessels) plays an important role in the progression of diabetic microvascular and macrovascular complications (**Fig. 1**). It is ascertained that anti-neutrophil methods of therapy retard and depress the progression of insulitis and autoimmune diabetes (Huang, Xiao, Xu, & Zhou, 2016).

Autoimmune processes start years before clinical diagnosis. The destruction of β-cells proceeds subclinically as insulitis for several months or years. Insulitis escalates with the course of time until a significant part of β-cells are destroyed (lose functional activity). The clinical period of the disease is detected when 80–95 % of the functioning β-cells have collapsed. At this stage, blood glucose levels increase, which is a clinical manifestation of DM.

An impaired secretion of insulin causing metabolic disorders is the background for the development of the symptoms accompanying type 1 DM. Insulin deficiency causes a decrease in the uptake and utilization of glucose by insulin-dependent tissues. Because of that, energy deficiency is developed in cells; glucose is stored in the interstitial space and blood, and hyperglycemia occurs. Mechanisms of intensified glycogenolysis and high-yield gluconeogenesis (glucose synthesis from protein and lipid metabolism intermediates) are simultaneously turned on to reduce the energy deficit in the cells. The degradation of proteins is followed by a depletion of protein pool of the organism, the immune status violation and a negative nitrogen balance. All of those alterations in the metabolic profile lead to an additional glucose flow to blood. However, glucose generated under such conditions is not absorbed by cells and contributes to an even more considerable hyperglycemia (Kitabchi, Umpierrez, Miles, & Fisher, 2009).

Conditions of hyperglycemia and metabolic disorders that occur during DM progression increase the risk of microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (diseases of peripheral arteries, ischemic diseases, congestive heart failure, myocardial infarction, stroke) complications (Zhang *et al*., 2020). Complications in DM are heterogenic and multifactorial. An important element contributing to the inclination of patients with DM to emerging complications, concomitant illnesses and inflammation in infectious diseases are alterations of structural and functional blood cell activity (Sybirna, Barska, & Gryshchuk, 2004).

2. Changes in the structural and functional state and metabolic profile of blood leukocytes in diabetes mellitus. Patients with DM are often diagnosed with bacterial and fungal infections, which are difficult to treat and cause general impairment

in the homeostasis of all systems. Functional state of leukocytes is one of the main factors of nonspecific and specific resistance of an organism. Leukocytes act as cells of the first line of defense in blood; their weakened functional activity promotes susceptibility to infections and severity of diabetes (Alba-Loureiro *et al*., 2007).

Diabetes mellitus is characterized by chronic systemic inflammation, which results in an activation of leukocytes and their recruitment to various organs. The interaction between neutrophils and endothelial cells is one of the first steps of inflammation development. Polymorphonuclear granulocytes in DM have an impaired adhesion, migration, chemotactic and phagocytic ability. In particular, neutrophils are characterized by an increased proinflammatory activity and degranulation, a decreased phagocytic and, respectively, antimicrobial activity; an impaired respiratory burst; inhibition of calcium-dependent signaling pathways and ectopic ATP-synthase activity. An increased adhesion of leukocytes in DM was also shown, which, however, is caused by blood plasma properties and a dysfunction in blood vessel endotheliocytes, and is not related to the properties of neutrophils, that have a weaker separate and cell-to-cell adhesion (Huang *et al*., 2016).

Mechanisms, which mediate pathological leukocyte-endothelial cell adhesion, include elevated exposure of cellular adhesion molecules on the surface of endothelial cells and alterations in the leukocytes (Zdioruk, Brodyak, & Sybirna, 2001). An increased membrane rigidity and a decreased deformation ability of leukocytes may cause injuries of capillaries. A small diameter of the vascular lumen, an enhanced adhesion of leukocytes to endothelial wall lead to their entrapment in capillaries (leukostasis) and an increased vessel occlusion, which is an important factor in the development of diabetic microangiopathy (Bajpai, & Tilley, 2018; Chibber, Ben-Mahmud, Chibber, & Kohner, 2007).

In response to chronic hyperglycemia, leukocytes switch to a subactivated state. It induces local release of various effector molecules, such as reactive oxygen/nitrogen species (ROS/RNS), cytokines, chemokines by activated leukocytes, which might potentially lead to endothelial cell and adjacent tissue damage, contributing to persistent inflammation. Proinflammatory cytokines regulate main anabolic pathways participating in insulin signal transmission and deteriorate glucose homeostasis (Huang *et al*., 2016). For instance, TNF-α, one of the cytokines mostly secreted by activated macrophages, is able to inhibit expression of important genes involved in glycemic control, such as GLUT-4 glucose transporter. Due to an impaired glucose transport into the cells, glycolytic pathway in leukocytes is inhibited, e.g. a decreased phosphofructokinase activity leads to elevated concentrations of glucose-6-phosphate, hydrogen and lactate ions (Graves, 2008).

A positive correlation between polyol pathway and leukocyte dysfunction is observed. The key enzyme of this pathway, NADPH-dependent aldose reductase, catalyzes reduction of glucose to sorbitol, which is further oxidized to fructose by NAD^+-dependent sorbite dehydrogenase (**Fig. 2**). Polyol pathway activation results in the deficiency of intracellular NADPH and an excessive amount of NADH, in other words, in redox imbalance. Reduced NAD^+ is a source of electrons in complex I of electron transport chain, which leads to an increased $O_2^{\bullet-}$ generation in mitochondria (Ayepola, Brooks, & Oguntibeju, 2014; Giacco, & Brownlee, 2010). Another direct negative consequence of sorbitol pathway hyperactivation includes intracellular sorbitol accumulation, which leads to an increased intracellular osmolarity and osmotic stress development (Obrosova, 2005).

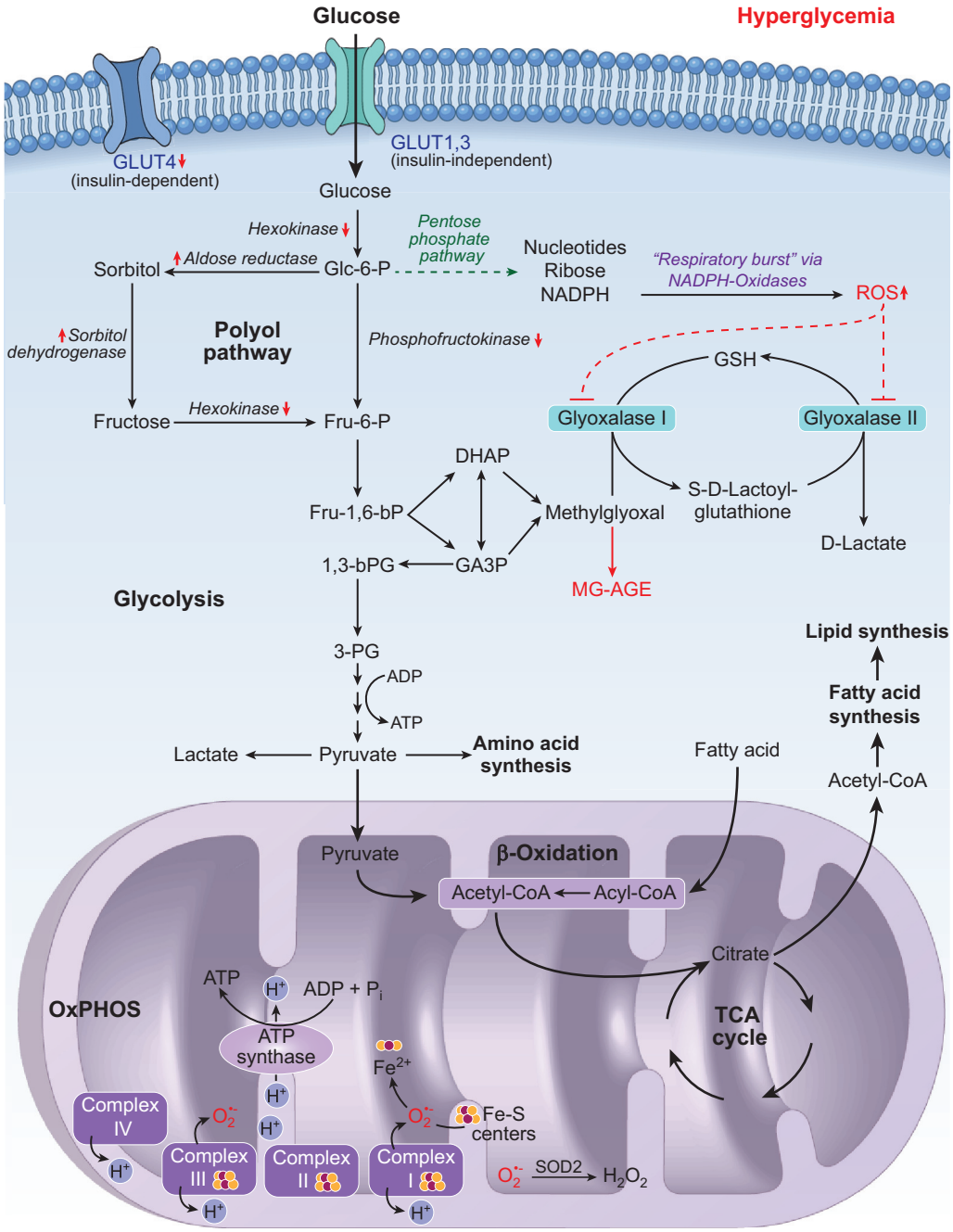

Fig. 2. Metabolic profile of leukocytes under type 1 diabetes mellitus: GLUT – glucose transporter; Glc-6-P – Glucose 6-phosphate; Fru-6-P – Fructose 6-phosphate; Fru-1,6-bP – Fructose 1,6-bisphosphate; DHAP – dihydroxyacetone phosphate; GA3P – glyceraldehyde-3-phosphate; 1,3-bPG – 1,3-bisphosphoglycerate; 3-PG – 3-phosphoglycerate; NADPH – nicotinamide adenine dinucleotide phosphate; TCA – tricarboxylic acid cycle; OxPHOS – oxidative phosphorylation; GSH – glutathione; MG-AGEs – methylglyoxal-derived AGEs

Apart from an enhanced polyol pathway, other major metabolic changes, caused by hyperglycemia, are overproduction of free radicals, reduced oxidative stress resistance of leukocytes and glycation of biomolecules (Alba-Loureiro *et al*., 2007; Bila, Dzydzan, Brodyak, & Sybirna, 2019).

Release of ROS by leukocytes is an important part of innate immunity and is essential for the normal antibacterial potential of cells. However, overproduction of ROS by leukocytes may cause damage of endothelium and adjacent tissues (Graves, 2008). Mitochondria are one of the main endogenous ROS sources. Electron transport across complexes I, III, IV, under physiological conditions is accompanied by proton flow from matrix to the intermembrane space, creating a proton gradient, which activates ATP synthase. On the contrary, an enhanced TCA cycle is observed in condition of diabetes in leukocytes with high intracellular acetyl-CoA content that leads to an increased electron flow from NADH and $FADH_2$ to the electron transport chain. As a result, membrane potential rises, reaching a critical threshold. At this moment, electron transfer to complex III is blocked, and, as a consequence, electrons return to coenzyme Q. A constant leakage of electrons and transfer to oxygen leads to superoxide anion radicals formation (**Fig. 2**) (Giacco, & Brownlee, 2010). This radical induces structural aberrations in Fe-S centers of complexes I-III, such as Ferrum ions oxidation by free radicals. Consequently, there is an imbalance between the respiratory chain functioning and conjugated oxidative phosphorylation.

In phagocytes (macrophages and neutrophils), ROS generation as a part of the innate immune response to pathogens, is mediated by NADPH-oxidase (Bedard, & Krause, 2007). This enzyme catalyzes electron transfer from NADPH to molecular oxygen with the formation of superoxide radical. Generation of $O_2^{\bullet-}$ leads to an increased amount of H_2O_2 in the reaction catalyzed by superoxide dismutase (**Fig. 2**). H_2O_2 is considered a nonradical and weak oxidant with a relatively long half-life which easily diffuses between cells and through cellular membranes (Kerksick, & Zuhl, 2015). Most of the generated H_2O_2 with the assistance of neutrophil myeloperoxidase, in turn, is transformed to hypochlorous acid (HOCl), which is a powerful oxidant (Gryszczyńska *et al*., 2017). Hydrogen peroxide may be additionally reduced to hydroxyl radical ($^{\bullet}OH$) either in Fenton reaction (when iron ions are available) or in Haber–Weiss reaction (Kerksick, & Zuhl, 2015).

Overproduction of ROS induces oxidation of cellular biomolecules (proteins, nucleic acids, membrane lipids) and corruption of their structure and function (Zhang *et al*., 2020). Free radicals have not only a direct detrimental effect, but they also may indirectly damage cells utilizing activation of several stress-sensitive intracellular signaling pathways: address the flow of glucose (and other monosaccharides) to polyol pathway; entail advanced glycation end-products (AGEs) generation and expression of receptors for AGEs (RAGEs) in addition to protein kinase C (PKC) activation and an enhanced hexamine pathway (Giacco, & Brownlee, 2010).

Since leukocytes require energy for their functioning, metabolic alterations can be involved in appearance of various disorders, observed in diabetic conditions (Alba-Loureiro *et al*., 2007). For instance, reduced bactericidal abilities of leukocytes and phagocytosis dysfunctions under DM are related to changes in lipid metabolism (metabolism of arachidonic acid in particular), deficient energetic maintenance of cells and direct aberrations in cytoskeleton functioning (Brodyak, Bila, & Sybirna, 2017; Chibber *et al*., 2007).

3. AGE-RAGE signaling mechanisms in pathogenesis of diabetes mellitus and its complications. The ability of glucose or other reducing sugars to interact with proteins and lipids is another important aspect in understanding leukocyte dysfunction pathogenesis and inflammatory defections in diabetes. The products of this non-enzymatic reaction called advanced glycation end-products (AGEs) are associated with the development of prolonged diabetic complications. It is worth mentioning that AGEs and their precursors are generated under physiological conditions at levels, lower than under DM (Chen *et al*., 2018).

Generation of AGEs is a complex molecular process that consists of 3 main stages. During the classic Maillard reaction, electrophilic carbonyl groups of glucose or other reactive monosaccharides interact with free amino groups of amino acids or amino acid residues of proteins (especially lysine and arginine), creating unstable aldimine compounds – Schiff's bases. Further rearrangement (acid-base catalysis) leads to the formation of more stable ketoamines – Amadori products (α-dicarbonyls) (**Fig. 3**) (Khan, Yee Ooi, Parvus, Valdez, & Tsin, 2020). Schiff bases and Amadori products are reversible reaction products. Nonetheless, they can irreversibly react with amino acid residues of peptides and proteins, creating protein adducts or protein crosslinks (Ahmed, 2005).

The most common agents of glycation in biological systems are glucose, fructose, maltose, mannose, arabinose, galactose, because they are relatively abundant in living organisms. However, monosaccharides differ in glycation ability. Glucose is considered one of the least active carbohydrates that participate in the Maillard reaction under physiological conditions (Boyarska, 2019). However, fructose, overproduced under polyol pathway hyperactivation, is a 10-fold more powerful glycation agent than glucose.

At the second stage, Schiff's bases and Amadori products transform to reactive dicarbonyl compounds, such as glyoxal, methylglyoxal and 3-deoxyglucosone, as a result of dehydration, oxidation and fragmentation of glycolytic intermediates (glyceraldehyde-3-phosphate and dihydroxyacetone phosphate), and other chemical reactions (**Fig. 3**) (Khan *et al*., 2020; Singh, Bali, Singh, & Jaggi, 2014). The formation of AGEs by autooxidation of Amadori products is known as the Hodge pathway. Moreover, reactive carbonyl compound generation is possible not only from Amadori products, but also as a result of lipid and amino acid degradation, dicarbonyl compound dissociation from aldimines (Namiki pathway), and carbonyl compound synthesis during glucose, ribose, fructose and glyceraldehyde autooxidation (Wolff pathway, **Fig. 3**) (Ott *et al*., 2014).

The final stage is represented by cyclization with a subsequent irreversible formation and accumulation of AGEs (**Fig. 3**). The intensity of the reaction depends on monosaccharide concentrations, reactivity of amino groups, half-life and concentration of proteins (Ahmed, 2005).

An accelerated formation of AGEs can also be caused by various pathological conditions, including hyperglycemia and oxidative stress under diabetes. Some metal ions (e.g., Copper) can enhance glycation of proteins and initiate glycoxidation in condition of oxidative stress (Marques *et al*., 2017).

The content of AGEs depends not only on the rate of their formation, but also on an organism's ability to excrete them using internal detoxifying pathways. Reduced glutathione, involved in glyoxal and methylglyoxal conversion to less toxic D-lactate, is one of the compounds participating in the process of AGEs detoxication (**Fig. 2**) (Schmoch *et al*., 2017). Other mechanisms include recruitment of enzymes – fructose aminases, which phosphorylate Amadori products, leading to their destabilization and spontaneous breakdown (Perrone, Giovino, Benny, & Martinelli, 2020).

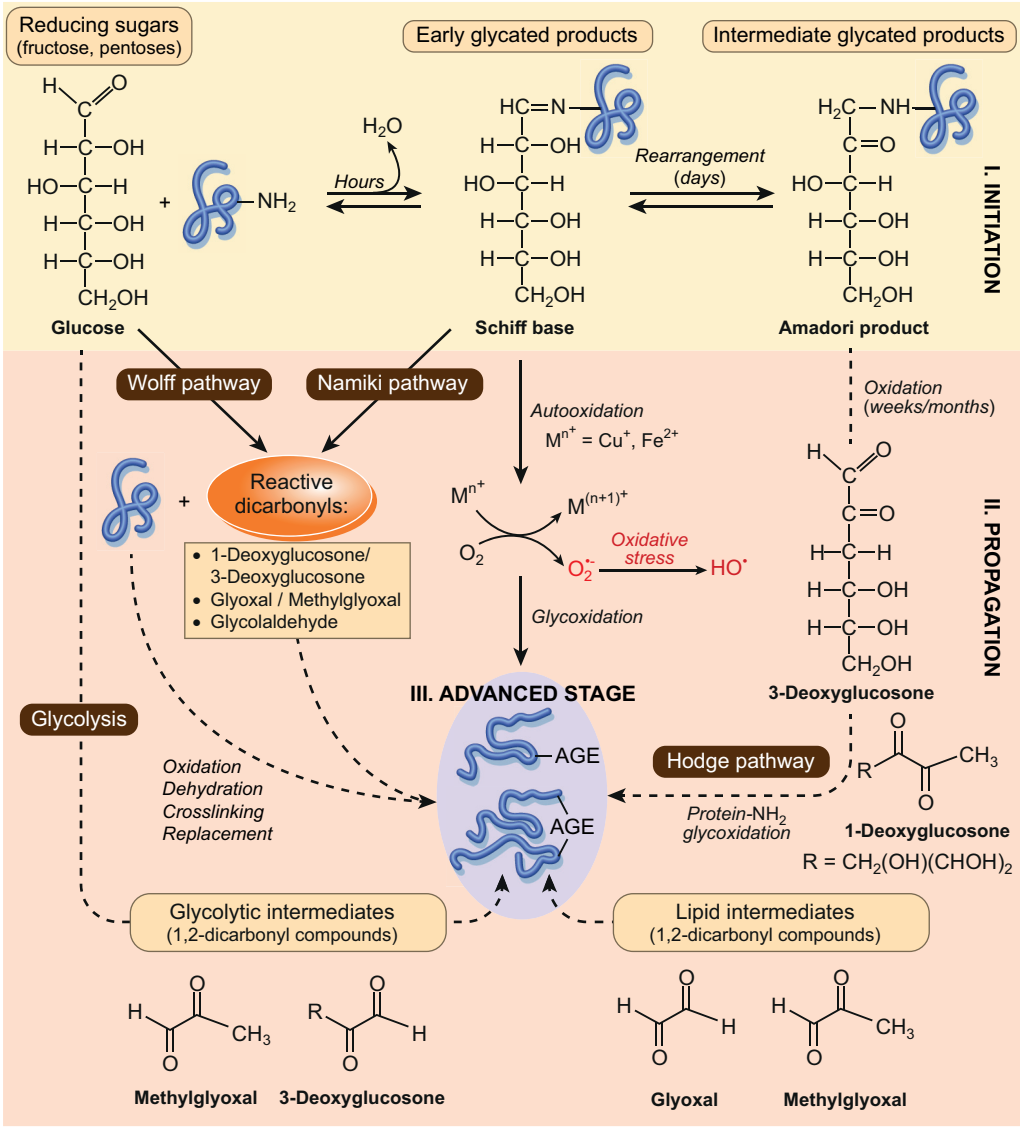

Fig. 3. Mechanism and pathways of advanced glycation end-products (AGEs) formation. The initial nonenzymatic interaction between a highly reactive carbonyl group of reducing sugars with a free amino group of proteins creates a reversible Schiff base, which spontaneously undergoes rearrangement into a partially reversible Amadori product. Highly reactive carbonyl intermediates can be formed by autooxidation of monosaccharides (Wolff pathway) or from Schiff's base (Namiki pathway) or from Amadori products (Hodge pathway). The highly reactive intermediates formed by these three pathways can react with free amino groups to create a variety of AGEs

Recently, many AGEs were identified as compounds with various chemical structures. Taking into account their physical and chemical properties, AGEs are fluorescent or nonfluorescent heterocyclic yellow-brown insoluble adducts, present in proteins with a long half-life, altering their physiological functions. Advanced glycation end-products

can be classified into several groups according to their ability / inability to emit fluorescence and form protein-protein crosslinks (**Fig. 4**) (Perrone *et al*., 2020; Song, Liu, Dong, Wang, & Zhang, 2021).

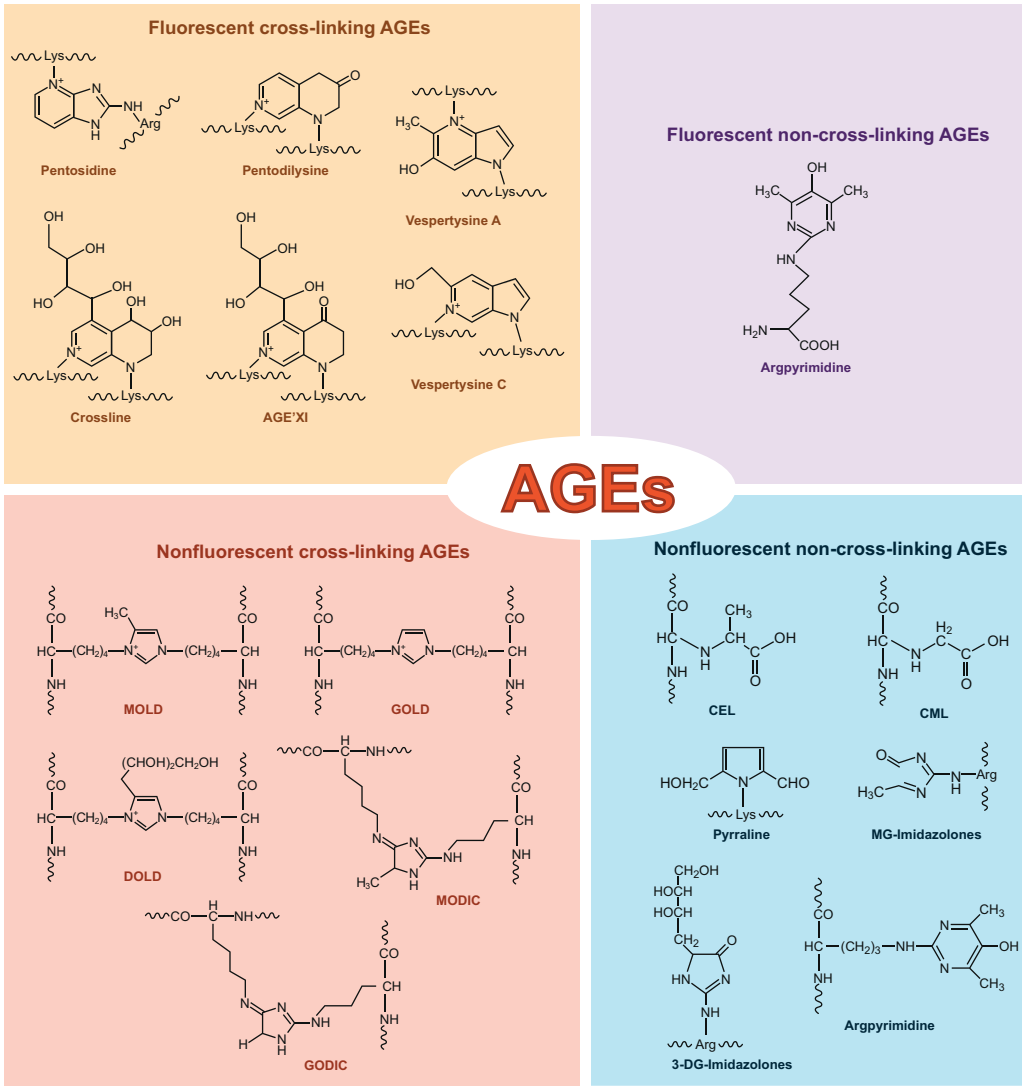

Fig. 4. Classification of AGEs groups based on their chemical structures and ability to emit fluorescence

The main described fluorescent AGEs that form protein-protein crosslinks are pentosidine, pentodilysine, AGE-XI, vespertysine A and vespertysine C. Pentosidine content may be considered the major advanced glycooxidation end-product; therefore, it is widely used as a marker of AGEs accumulation in plasma and other tissues. Pentosidine is formed by crosslinking of arginine and lysine residues joined by a pentose molecule. Other AGEs, which form protein crosslinks but are not fluorescent, have also been identified. These compounds include glyoxal-lysine dimer (GOLD) and methylglyoxal-lysine

dimer (MOLD), which are generated in a reaction between two side chains of lysine and two glyoxal molecules, respectively. Other related cross-links of arginine, such as imidazolium cross-links derived from glyoxal and lysine-arginine (GODIC) or from methylglyoxal and lysine-lysine (MODIC), have been isolated from bovine serum albumin.

Nonfluorescent AGEs not forming crosslinks, involved in pathogenesis of diabetes, inflammation and other diseases, include carboxymethyllysine (CML), carboxyethyllysine (CEL), pyrraline and imidazolones. In addition, blood of patients with DM contains a number of fluorescent AGEs not forming crosslinks. They are similar in structure to fluorescent AGEs, except for the one bond joining the heterocyclic part with an amino acid and replaced with a NH-bond (Perrone *et al*., 2020; Song *et al*., 2021).

The effect of AGEs on an organism is mediated by their interaction with specific receptors. The most studied AGE-binding receptors are: the multi-ligand receptor for AGEs (RAGE); the AGE-receptor complex (AGE-R1/OST-48 (oligosaccharyl transferase-48), AGE-R2/80K-H (80K-H phosphoprotein), AGE-R3/galectin-3) and some members of the scavenger receptor (SRs) family (SR-A; SR-B: CD36, SR-BI, SR-E: LOX-1; FEEL-1; FEEL-2). Cellular receptors for AGEs can be classified into two types: receptors binding AGEs and initiating various signaling pathways, and receptors interacting with AGEs and causing their breakdown. For example, such receptors as AGE-R1, AGE-R2, AGE-R3, and class A macrophage SRs have an ability to bind AGEs, but do not transmit the intracellular signal after they interact with a ligand. Instead, they can promote clearance and possible detoxification of AGEs. Some SRs (SR-A, SR-B, SR-E) and FEEL scavenger receptor type 1 and 2 (fasciclin, EGF-like, laminin-type EGF-like, and link domain-containing scavenger receptor-1 (FEEL-1) and FEEL-2) – are also able to bind AGEs (Oliveira *et al*., 2013; Ott *et al*., 2014).

The AGEs' receptor with the most detailed description is RAGE. It is a multiligand glycoprotein type 1 receptor with a molecular weight of 45-55 kDa. RAGE belongs to the immunoglobulin family (Qin, Goswami, Dawson, & Dawson, 2008). It is a pattern recognition receptor, which, apart from AGEs, also binds S-100/calgranulins, amphoterin B1, transthyretin, leukocyte integrins, macrophage antigen-1 (Mac-1), DAMPs (damage-associated molecular patterns), β-amyloid peptides and fibrils.

In the structure of RAGE, there is an extracellular domain containing one V-type and two C-type immunoglobulin regions, a single hydrophobic transmembrane domain and a short cytoplasmic tail, which is important for signal transduction from RAGE (**Fig. 5**) (Zhang *et al*., 2008).

Apart from RAGE expressed in cell membranes (also known as full-length RAGE – flRAGE), several other isoforms of the receptor were described, mainly its soluble form RAGE (sRAGE). sRAGE contains the same V- and C-domains found in flRAGE, but it does not have a transmembrane domain and a cytosolic tail (**Fig. 5**). Two types of sRAGEs have been investigated: esRAGE (endogenous secretory RAGE, also known as sRAGE_v1) and cRAGE (cleaved RAGE) (Oliveira *et al*., 2013). cRAGE forms as a result of flRAGE cleavage by metalloproteases (ADAM10 and MMP9). esRAGE is formed by alternative splicing of intron 9 with exon 10 deletion from mRNA, which shifts transcript's reading frame. It leads to the appearance of stop codon in intron 9, which would correspond to the transmembrane domain and cytosolic tail of full-length RAGE in translation. As a result, a soluble RAGE isoform is formed (Hudson *et al*., 2008). Nevertheless, cRAGE generated by proteolytic cleavage is the dominant isoform in human blood (Raucci *et al*., 2008).

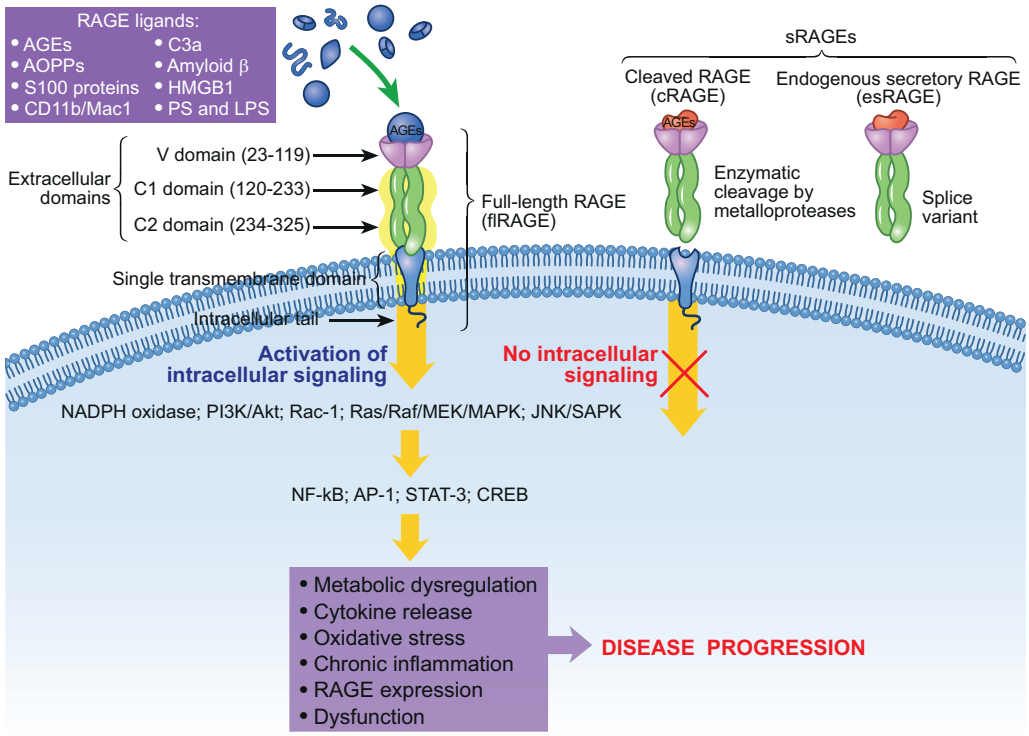

Fig. 5. Receptor for advanced glycation end-product (RAGE) structure: AGEs – advanced glycation end-products; AOPPs – advanced oxidation protein products; S100s – S100 family proteins; CD11b/Mac1 – Integrin αM / Macrophage-1 antigen; C3a – Complement component 3a; HMGB1 – High mobility group protein (B)1 (amphoterin); PS – Phosphatidylserine; LPS – Lipopolysaccharide; sRAGE – soluble RAGE

RAGEs are expressed in endothelial cells, mononuclear phagocytes, hepatocytes, lymphocytes, vascular smooth muscle cells, glomerular cells and neurons. Lung tissue has the highest rates of RAGE expression (Buckley, & Ehrhardt, 2010; Lindsey, Cipollone, Abdullah, & McGuire, 2009). Under physiological conditions, RAGEs are expressed at low levels in tissues and vessels, however it is self-regulated by RAGE interaction with ligands through the mechanism activated by intracellular redox processes. For instance, tissues, in which deposition of proinflammatory ligands, enhanced cell activation or stress occur, have significantly higher RAGE expression (Oliveira *et al.*, 2013).

4. Signal transduction during AGE-RAGE interaction in leukocytes under physiological and pathological conditions. Generation of AGEs is an irreversible process of glycation products formation in the circulatory system and other tissues where long-lived proteins (collagen, elastin) are present. However, AGEs can also form crosslinks with short-lived proteins, such as albumin (Rungratanawanich, Qu, Wang, Essa, & Song, 2021). It has been ascertained that glycation of albumin, fibrinogen and globulins causes altered drug binding in plasma, induces platelet activation, ROS generation, impaired fibrinolysis and immune system regulation (Singh *et al.*, 2014).

AGEs and their precursors may provoke immune cell damage through several common mechanisms. First, protein glycation leads to changes in their functioning.

Second, components of extracellular matrix modified by AGEs' precursors interact abnormally with other matrix components and receptors (integrins) exposed on the surface of leukocytes.

Protein glycation is one of the factors causing alterations at leukocyte-endothelial interaction and chemotaxis under DM (Sannomiya, Oliveira, & Fortes, 1997). In particular, glycated proteins extracted from DM rat serum reduce leukocyte membrane fluidity when administered to control animals and affect migration ability of the cells (Masuda, Murakami, Egawa, & Murata, 1990).

The main mechanism of AGEs' effect is their interaction with specific cell surface receptors. Ligand binding to RAGE enhances various signaling pathways by activating Ras/Raf/MEK/MAPK, phosphatidylinositol-3′-kinase (PI3K), JNK/SAPK (c-Jun-N-terminal kinase/Stress – activated protein kinase, **Fig. 5**) (Bierhaus *et al*., 2005). These signaling cascades control NF-κB that leads to further transcription of many genes of proinflammatory pathways and expression of adhesion molecules, growth factors, proinflammatory cytokines, participating in the pathogenesis of diabetic complications (**Fig. 5**). Advanced glycation end-products bind to the receptors and, thus, can directly stimulate ROS generation assisted by NADPH-oxidases (**Fig. 5)**, and/or other mechanisms (activation of mitochondrial respiratory chain, microsomal enzymes, xanthine oxidase and arachidonic acid metabolism enzymes) (Wautier *et al*., 2001; Ott *et al*., 2014). At the same time, AGE-RAGE interaction leads to a decrease in GSH and ascorbic acid contents, and, therefore, contributes to enhancement of intracellular oxidative stress. Moreover, GSH pool depletion determines a reduced recirculation and activity of glyoxalase 1 – enzyme, which plays an important role in preventing intracellular AGEs production (**Fig. 2**) (Bierhaus *et al*., 2005). This disrupts antioxidant defence and biological processes in leukocytes.

RAGE is a key molecule in monocyte activation and differentiation. Monocytes express membrane-bound RAGEs and sRAGEs. For example, AGEs binding to RAGEs on the surface of these cells induces the secretion of proinflammatory cytokines (IL-6, CXCL8, IL-12) and chemokines (TNF, IL-1, CCL2). Macrophages, like monocytes, expose RAGEs on their cell surface. Ligand that binds to RAGE on macrophages induces proinflammatory phenotype similar to M1-macrophage group. Cellular response to RAGE activation is highly regulated and depends on the nature of ligand and the level of monocyte/macrophage differentiation. T- and B-lymphocytes express RAGE as well as dendritic cells, which represent the connection between the innate and adaptive immune system. Receptors for AGE play an important role in adhesion and movement of these cells into the site of inflammation.

T-cells show a lower RAGE expression in comparison with other leukocytes. Naïve T-cells differentiation into effector cells is triggered by TCR (T-cell receptor) activation and signals from APC. Under physiological condition, naïve T-cells do not express RAGEs. However, RAGEs are exposed by $CD4^+$ and $CD8^+$ effector cells in the same way as corresponding $CD4^+$ memory cells. It has been also confirmed that RAGEs are essential for APC-dependent primary T-cell activation.

Receptors for AGE are exposed on neutrophil surface and interact with ligands, which leads to an abrupt elevation of intracellular Ca^{2+} concentration and actin polymerization. On the one hand, it induces a higher phagocytic ability of neutrophils; on the other hand – a lower intracellular killing ability. Receptors for AGE control the migration of neutrophils across intestinal epithelium, mediating the adhesion of neutrophils by binding with the integrins on their surface (Alba-Loureiro *et al*., 2007).

Transduction of intracellular signal from AGE/RAGE complexes enhances diapedesis of leukocytes from blood to tissues. High AGE levels caused by hyperglycemia result in leukocyte hyperactivation and may assist the progress of inflammation or concomitant autoimmune diseases. The ligand-RAGE interaction on leukocytes surface is involved in an acute inflammatory response. Importantly, maintaining RAGE signaling increases inflammation and leads to the development of chronic inflammatory disorders.

CONCLUSION

Specific ligands, in particular an increased content of AGEs in blood plasma, enhance the exposure of RAGEs on the membranes of leukocytes under DM. The RAGE-ligand interaction activates the transcription factor NF-κB, which stimulates the formation of proinflammatory molecules, and, importantly, RAGEs themselves. This creates a positive feedback loop, which leads to leukocytes activation. Hence, RAGE expression is closely associated with the progress of inflammatory response, which induces chronic infectious processes typical of diabetes.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

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ЗМІНИ, ЯКИХ ЗАЗНАЮТЬ І ЗУМОВЛЮЮТЬ ЛЕЙКОЦИТИ ЗА ЦУКРОВОГО ДІАБЕТУ 1 ТИПУ

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Лейкоцити є невід'ємним компонентом імунного процесу, який реалізується на клітинному та гуморальному рівнях. Ці клітини безпосередньо ініціюють й аутоімунні процеси і розлади. Цукровий діабет – одне із найпоширеніших аутоімунних захворювань, розвиток якого опосередковується складними механізмами міжклітинної комунікації, у якій лейкоцити є ключовою ланкою, відіграючи роль як ефекторів, так і регуляторів. Окрім того, імунокомпетентні клітини теж зазнають діабетичного впливу, посиленого хронічною гіперглікемією. Зокрема, продукти неензиматичної взаємодії глюкози або інших редукуючих моносахаридів із молекулами білків або ліпідів – кінцеві продукти глікації – причетні до розвитку довготривалих негативних змін за діабету. Зв'язуючись зі специфічними клітинними рецепторами, вони індукують внутрішньоклітинні сигнальні шляхи, що призводять до посилення експресії генів прозапальних цитокінів та, як наслідок, до діабетичних ускладнень. З огляду на це, за цукрового діабету 1 типу, як ключового проблемного питання охорони здоров'я у всьому світі, деталі патогенезу якого досі не з'ясовані, важливо аналізувати й досліджувати метаболічні та функціональні зміни у лейкоцитах, особливо зумовлені кінцевими продуктами глікації і рецепторами до них.

Ключові слова: цукровий діабет 1 типу, лейкоцити, кінцеві продукти глікації, рецептори до кінцевих продуктів глікації

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