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IMMUNOMODULATORY ENZYMES AND DIABETES

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Summary. *Immunomodulatory ectoenzymes are proteins localized on cell membranes, with active sites exposed to the extracellular surface, involved into cell-to-cell communication, cellular growth and differentiation processes. Alterations of their activity are found in both type 1 and type 2 diabetes, thus attracting a growing interest in their investigation. PC-1 (an enzyme with alkaline phosphodiesterase/nucleotide pyrophosphatase activity) inhibits the insulin receptor tyrosine kinase activity by direct binding to the insulin receptor a subunit, thereby representing a key suspect for impaired insulin signaling in obese insulin resistant type 2 diabetics. Overexpression of PC-1 was found in various tissues of type 2 diabetics, as well as in obese insulin resistant rhesus monkeys, confirming its role in pathogenesis of insulin resistance. Oral treatment with metformin was found to decrease a level of PC-1 in cultured lymphocytes of type 2 diabetics, thus suggesting a possible mechanism of metformin action in target tissues. Other immunomodulatory enzymes reviewed in this article (5'-Nu, DPP IV, APN) also play an important role in understanding of diabetes and progression of its complications. A certain progress has been made in the therapeutic aspect with DPP IV inhibitors, while APN and 5'-Nu could be useful in recognition of diabetic complications. Therefore further investigations of the relation between immunomodulatory enzymes and pathogenesis of diabetes would be of great benefit for both diabetics and clinicians dealing with diabetes.*

Key words: *Immunomodulatory enzymes, PC-1, DPP IV, 5'-nucleotidase, diabetes, insulin resistance*

Introduction

Immunomodulatory ectoenzymes are proteins localized on cell membranes with active sites exposed to the extracellular surface, involved into cell-to-cell communication, cellular growth and differentiation processes (1). Ectopeptidases regulate activation and decay of biologically important peptides, including hormones, cytokines, vasoactive peptides, and thereby changing the local concentration of active peptides. They regulate the cell activation process, its proliferation, adhesion, matrix synthesis, and signal transduction under various physiological and pathological conditions (2). Investigations have shown that certain immunomodulatory enzymes (dipeptidyl-peptidase IV, aminopeptidase N, alkaline phosphodiesterase I and 5' – nucleotidase) play significant role in the pathogenesis of diabetes, especially in insulin-resistance found in type 2 diabetes (3).

General characteristics of immunomodulatory enzymes investigated in diabetes

Dipeptidyl-peptidase IV (DPP IV, EC 3.4.14.5) releases N-terminal peptides from oligopeptides with proline or alanine as penultimate amino acid. In hemopoietic cells, DPP IV is predominantly bound to the surface of CD4 positive cells, and its enzymatic activity increases with T-cell activation (4). DPP IV is identified as a CD26 surface marker in lymphocytes (5). It is suggested that this membrane protease is involved in induction and activation of cytokines, which are controlling lymphocyte proliferation (6). Inhibition of DPP IV by two potent inhibitors of peptidyl-boroic acid suppresses antigen-specific T-cell proliferation in vitro. Injection of these inhibitors to BALB/c mice decreases the activity of DPP IV after immunization, which directly proves the important role that DPP IV plays in *in vitro* immune response (4).

Amino peptidase N (APN, EC 3.4.11.2) cleaves bioactive oligopeptides with N-terminal neutral amino acids. It is an amino peptidase, a non-organ-specific hydrolytic enzyme acting on peptides NH_2 –terminus (5). These enzymes play an especially important role in hemopoietic cells, malignant hemopathies and immunology disorders. APN is a 150 kDa glycoprotein, identical to the CD13 cell marker, whose primary structure was identified by normal and malignant myeloid cell DNA sequencing (7). According to these findings, APN is a membrane protein consisting of 967 amino acids with an extracellular domain containing pentapeptide sequence. That sequence is a catalytic site for zinc-binding metalloproteases. APN also contains a 24-aminoacid hydrophilic segment nearby N-terminal ending anchored into the cell membrane. In most species, CD13 is a homodimer, with its function depending on the lo-

calization. A frequent colocalization and cooperation of CD13 with CD26 (DPP IV) or CD10 during the protein degradation process is found. APN exerts its effect on various substrates, including endorphin, encephalin, somatostatin, etc (8). Likewise CD26, CD13 is considered to be a helper adhesive molecule.

Alkaline phosphodiesterase I (APD, EC 3.1.4.1) is a cell-surface enzyme, catalyzing hydrolysis of poliribonucleides with free 3'-OH group, followed by release of 5'-nucleoside monophosphate (9). Surface cell antigen PC-1, characteristic for murine B-cells in the late stage of differentiation, was identified as APD. PC-1 is an ectoenzyme, possessing both phosphodiesterase and nucleotide pyrophosphatase activity, whose physiologic function is unknown. According to the present theory, PC-1 is a member of an enzymatic cascade system involved in nucleotide and nucleic acid hydrolysis, which results in a formation of nucleoside taken by the nucleoside transporting system. The mechanism allows nucleotide utilization by cells unable for *de novo* synthesis (10). A polymorphism in the ecto-nucleotide pyrophosphatase/phosphodiesterase 1 gene (ENPP1, PC-1), resulting in an amino acid change from lysine to glutamine at codon 121 (K121Q), is associated with insulin resistance (11).

5'-nucleotidase (5'-Nu, EC 3.5.1.2.) is a plasma cell membrane enzyme, which catalyzes dephosphorilation of purine ribonucleoside and deoxyribonucleoside monophosphates. Extracellular NAD is degraded to the purine and pyrimidine metabolite by enzymes localized on cell surface, exposed in various degrees in different types of cells and tissues. In human peripheral blood lymphocytes, 5'-Nu is more active in B than in T lymphocytes, and seemingly does not exist in non-T, non-B (null) lymphocytes. Level of 5'-Nu varies depending on T-cell subpopulation, with bigger activity in Leu-2+/T8+ supressor/cytotoxic subpopulation than in T helper/inducer cells. Two other nucleotide-hydrolyzing enzymes are activated on T-cell surface together with CD38: human PC-1 molecule and nucleotidase producing adenosine from AMP, which is maybe different from CD73 5'-nucleotidase (12).

It seems that 5'-nucleotidase plays a key regulative role in the local adenosine concentration. Adenosine is a potent vasodilator as well as an immunosupressory and anti-inflammatory substance. It inhibits lymphocyte-mediated cell cytotoxicity and lecithin-stimulated lymphocyte proliferative response. It also decreases liberation of superoxide anions and hydrogen peroxide form stimulated neutrophils and protects vascular endothelium from damage caused by neutrophil leukocytes. It was confirmed that NAD glycohydrolaze, nucleotide pyrophosphatase and 5'-nucelotidase are located on the surface of human dermal fibroblasts (13). Nucleotide pyrophosphatase cleaves NAD to nicotinamide mononucleotide and AMP, followed by 5'-nucelotidase hydrolysis of AMP to adenosine. Adenosine is a product of NAD hydrolysis incorporated in cells, and further metabolized to the ATP (14).

Immunomodulatory enzymes and diabetes type 1

There is no doubt that pathogenesis of type 1 diabetes, in most cases, involves immune processes, leading toward a failure of b cell function and hyperglycemia. Current investigations suggest that immunomodulatory enzymes as regulators of immune response and cell functions have a marked role especially in the development of late complication of type 1 diabetes.

Albuminuria is found in insulin-resistant type 1 diabetics, thus connecting the presence of PC-1 glycoprotein amino acid variant, K121Q, with renal failure in diabetes (15). A small follow-up study of patients with type 1 diabetes and proteinuria suggests that renal function declines faster in carriers of the Q variant of PC-1 gene than in noncarriers (11). The risk of early-onset ESRD for carriers of the Q variant was 2.3 times greater that for noncarriers (95% CI, 1.2-4.6), while the Q variant was not associated with late-onset ESRD (11). The faster GFR decline in the patients carrying the Q allele could be the result of reduced sensitivity to the renoprotective effect of antihypertensive therapy, while PC-1 genotyping could identify type 1 diabetic patients with a more rapid progression of diabetic nephropathy.

In 30 diabetic children, metabolic control (HbA1C) and the duration of diabetes were directly correlated with the levels of DPP IV (16). DPP IV excretion was elevated in all diabetic patients. Significant correlations were not identified between urinary DPP IV excretion and the duration of diabetes and metabolic control (16). Activity of DPP IV is also important for the efficiency of GLP-1, which lowers blood glucose in both type 1 and type 2 patients and may be therapeutically useful for treatment of patients with diabetes. The short duration of action of GLP-1 may be accounted for in part by DPP-IV, which cleaves GLP-1 at the NH2-terminus; hence GLP-1 analogs or the lizard peptide exendin-4 that are resistant to DPP-IV cleavage may be more potent GLP-1 molecules *in vivo* (17).

Urinary excretion of APN was significantly higher in diabetics than in controls (18) but, although 3-30 fold increased in comparison to control, that increase was nonspecific for diabetic nephropathy (19). Its function in pathogenesis of diabetes is not yet known.

Drukker et al. (20) have found that the ratio of the activity of adenosine deaminase to that of 5'-nucleotidase correlating with the level of glycemia might be the most informative test in the diagnosis of the depth of the discovered metabolic disorders in alloxan diabetes. 5'-Nucleotidase was not different between insulin-treated and untreated hypertensive diabetic rats in investigation carried on by Chen et al (21). According to findings by Kwan, microsomal membranes isolated from the mesenteric arteries of diabetic BB rats showed increased alkaline phosphatase and 5'-nucleotidase activities compared to those isolated from the two groups of non-diabetic control rats, suggesting that in the spontaneously diabetic BB rats, alterations in both structural and functional parameters may

underline the vascular complications associated with type 1 diabetes mellitus in humans (22).

Immunomodulatory enzymes and diabetes type 2

The main feature of type 2 diabetes is insulin resistance, a complex state found also in other pathological conditions and healthy people (23). In insulin resistance, target tissues are not capable of normal response to insulin in circulation. Molecular mechanisms of insulin resistance are only partially clarified and are closely related to the complete understanding of the insulin signal transduction process and insulin effects in target tissues. Recently, PC-1 and other immunomodulatory enzymes were given a great importance in modification of insulin receptor function. Goldfine et al. consider PC-1 as one of the most prominent pathogenetic factors of insulin resistance (24). Enzymatic activity of PC-1, identified as a cleavage of sugar phosphates, pyrophosphates and phosphodiesterase bonds, involves threonine residue on the extracellular part of the molecule. Mutation in this segment of PC-1 does not prevent it from inhibition of insulin receptor (10).

Investigations suggest the presence of direct interaction between **PC-1** and insulin receptors, and the inhibitory effect of PC-1 on the insulin receptor tyrosine kinase activity (3). Activity of PC-1 is 7-9 times increased in type 2 diabetics (25). Mechanisms of PC-1 overexpression are unknown. Some results indicate the possibility that PC-1 genotyping could identify individuals who are at risk of developing insulin resistance, and suggest a cause-effect relationship between the Q carrying genotype and the insulin resistance phenotype and type 2 diabetes. A haplotype is identified in Sicilians in the 3'-untranslated region of the PC-1 gene that may modulate PC-1 expression and confer an increased risk for insulin resistance (26), as a possible molecular mechanism for PC-1 overexpression. On the contrary, in Danish Caucasians, the K121Q polymorphism of human PC-1 gene is not associated with type 2 diabetes or insulin resistance (27). The study in Finland and Sweden shows that, although the Q allele of the human glycoprotein PC-1 gene is associated with surrogate measures of insulin resistance, it may not be enough to increase the susceptibility to type 2 diabetes (28).

Several studies indicate that pregnant control and GDM subjects had increased PC-1 content and suggest excessive phosphorylation of serine/threonine residues in muscle insulin receptors and that both may contribute to decreased IRTK activity. These changes worsen in women with GDM when controlling for obesity. These postreceptor defects in insulin signaling may contribute to the pathogenesis of GDM and increased risk for type 2 diabetes later in life (29). Overexpression of PC-1 was found in dermal fibroblasts of insulin resistant subjects. In dermal fibroblast of Japanese type 2 diabetics, activity of PC-1 was significantly elevated over control values (30). A content of PC-1 in skeletal muscles and adipose tissue positively correlates to the general insulin sensitivity (24). In breast cancer cells, an overexpression of PC-1 is in correlation with inhibition of insulin receptor tyrosine kinase activity (31).

Experimental investigations suggest that, in addition to blocking insulin receptor kinase activation, PC-1 can also block insulin receptor signaling at a post-receptor site (32). According to these findings, PC-1 influences the activity of p70 ribosomal S6 kinase, thus decreasing several biologic effects of insulin, including glucose and amino-acid uptake (32). Plasma PC-1 was decreased in insulin resistant subjects in comparison with insulin sensitive non-diabetic subjects and correlated negatively to waist-to-hip ratio and mean arterial blood pressure, while a positive correlation was found between HDL/total cholesterol and M value and PC-1 in clamp studies (33). Frittitta et al. have suggested a posible clinical application of soluble PC-1 measurement, as an indicator of insulin resistant states (33).

DPP-IV degrades glucagon-like peptide 1 (GLP-1), a peptide with insulinotropic effect, presenting a potentially useful agent in the therapy of type 2 diabetes (34). The activity of GLP-1 is preserved in type 2 diabetes, although limited by short half-life (only 5 minutes) and degradation by DPP IV. The process results in formation of GLP-1 receptor antagonist metabolite, suggesting that inhibition of DPP IV could increase GLP-1 half-life in circulation (35). Experimental investigations on mice have shown that DPP IV inhibition results in improved glucose tolerance and insulin secretion (36). Investigation in cultured PMA-stimulated lymphocytes of type 2 diabetics has shown significantly increased activity of DPP IV, nevertheless it decreased after 3-month metformin treatment (37).

5'-Nu, as a zinc-dependent enzyme, is decreased in type 2 diabetics. Some investigations suggest that short-term zinc supplementation in diabetics could double the level of 5'-Nu, although its activity was maintained below control values (38). Theoretically, zinc can exert a number of indirect antioxidant functions, presenting 5'-Nu as a zinc-dependent enzyme as a marker of oxidative damage in diabetes, and indicator of chronic complication and vascular damage in diabetics.

Diabetes treatment and immunomodulatory enzymes

The major therapeutic problem in treatment of the newly diagnosed, obese type 2 diabetics is insulin resistance. PC-1 overexpression, as an important factor in pathogenesis of insulin resistant state, could be a target of antidiabetic treatment. Frequently used antihyperglycemic drug, metformine, was proven to be efficient since it significantly decreases the level of PC-1 in type 2 diabetics (37). Some new sensitizing agents are still investigated, e.g. TLK16998 and Merck L7, which improved IR autophosphorylation in cells with diminished IR signaling due to overexpression of membrane glycoprotein PC-1 (39).

DPP IV degrades extremely rapid GLP-1, which has been proposed as a new treatment for type 2 diabetes. Therefore, a treatment with GLP-1 should demand inhibition of DPP IV activity, which cleaves GLP-1 at the NH2-terminus, producing a metabolite that acts as an antagonist at the GLP-1 receptor (17, 34). Some specific inhibitors of DPP IV were tried in experimental studies, showing that DPP IV inhibition greatly ameliorates the condition (34). Thus, DPP IV inhibition may be an effective supplement to diet and exercise treatment in attempts to prevent the deterioration of glucose metabolism associated with Western lifestyle. In some reports, a minor modification in GLP-1 structure has proved successful in prevention of its degradation by DPP IV (35).

Diabetes mellitus may cause vulnerability to a moderate zinc deficiency (38). 5'-Nu, as a zinc dependent-enzyme, and an indicator of vascular oxidative damage, is a potentially useful marker of zinc status in diabetics. Zinc supplementation could be a potential way to increase reduced 5'-Nu in diabetics and thereby prevent or slow down progression of vascular damage in diabetes (38).

PC-1 as a marker of insulin-resistant state

Insulin resistance is an important element of type 2 diabetes pathogenesis. A major problem in type 2 diabetics is identification of insulin resistant state, since there are no reliable clinical indicators of insulin resistance yet. Determination of tissue or even better, plasma level of PC-1 could represent a possible solution of that problem. Determination of tissue concentration of PC-1 would be inconvenient for patients, since it requires a tissue biopsy. A soluble form of PC-1 was identified (26, 40) presumably produced by proteolytic cleavage of membrane PC-1 (10). Frittitta et al. in their investigation performed on non-diabetic insulin resistant subjects with a wide range of BMI varying from non-obese to extremely obese, have found that a decreased PC-1 in plasma could be a predictor of insulin resistant state (26). On the contrary, Stefanović et al (41) have shown a significant correlation between an increased level of PC-1 in plasma and cultured lymphocytes in type 2 diabetics. The inconsistence in these findings requires further investigations, which could help establishing PC-1 as a marker of insulin resistance.

Conclusion and implications

Diabetes mellitus represents one of major health and economical problems of the modern world. A changing lifestyle and "westernization" of less developed countries assign an diabetes an even greater importance. Insulin resistance, as a prominent feature of type 2 diabetes, attracts attention of numerous investigators worldwide. Molecular mechanisms of insulin resistance are not completely understood, although contribution of certain factors cannot be denied. PC-1 (an enzyme with alkaline phosphodiesterase/nucleotide pyrophosphatase activity) inhibits insulin receptor tyrosine kinase activity by direct binding to the insulin receptor a subunit, thereby representing a key suspect for impaired insulin signaling in obese insulin resistant type 2 diabetics. Overexpression of PC-1 was found in various tissues of type 2 diabetics, as well as in obese insulin resistant rhesus monkeys, confirming its role in the pathogenesis of insulin resistance. Oral treatment with metformin was found to decrease a level of PC-1 in cultured lymphocytes of type 2 diabetics, thus suggesting a possible mechanism of metformin action in target tissues. Insulin resistant state is related to the polymorphism in PC-1 genotype in some populations. However, this issue needs further investigation. A soluble form of PC-1 could find its clinical application in identification of insulin resistant state, and so far, it represents a greatest benefit to clinical practice.

Other immunomodulatory enzymes reviewed in this article (5'-Nu, DPP IV, APN) also play an important role in understanding diabetes and progression of its complications. Certain progress has been made in therapy with DPP IV inhibitors, while APN and 5'-Nu could be useful in the recognition of diabetic complications. Therefore further investigations would be of great benefit for both diabetics and clinicians dealing with diabetes.

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IMUNOMODULATORNI ENZIMI I DIJABETES

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Kratak sadržaj: *Imunomodulatorni enzimi su proteini ćelijske membrane sa ekstracelularnim aktivnim domenima, koji učestvuju u međusobnoj interakciji ćelija, procesu ćelijskog rasta i diferencijacije. Izmenjena aktivnost nekih imunomodulatornih enzima dovodi se u vezu sa patogenezom dijabetesa i njegovih hroničnih komplikacija. Naročiti značaj savremena iztraživanja pridaju PC-1 molekulu, enzimu koji poseduje aktivnost alkalne fosfodiesteraze I i nukleotid pirofosfataze, i koji inhibiše tirozin kinaznu aktivnost insulinskog receptora direktnim vezivanjem za njegovu alfa podjedinicu. Za razliku od insulinosenzitivnih dijabetičara i zdravih osoba, prekomerna ekspresija PC-1 nađena je u ciljnim tkivima gojaznih, insulinorezistentnih tip 2 dijabetičara, kao i kod gojaznih insulinorezistentnih rezus majmuna, što ukazuje na ulogu PC-1 u patogenezi insulinske rezistencije. Oralna terapija metfominom smanjuje limfocitnu aktivnost PC-1 kod tip 2 dijabetičara, što ukazuje na mogući mehanizam delovanja metformina na nivou ciljnih tkiva. Drugi imunomodulatorni enzimi koji mogu imati značaja u patogenezi dijabetesa su DPP IV, 5'-nukleotidaza i APN. Postoje istraživanja vezana za terapijsku upotrebu DPP IV inhibitora, dok APN i 5'-Nu mogu koristiti u otkrivanju komplikacija dijabetesa. Literaturni podaci pokazuju da dalja istraživanja uloge imunomodulatornih enzima u nastanku dijabetesa i njegovih komplikacija mogu biti od velikog fundamentalnog i praktičnog značaja.*

Ključne reči: *Imunomodulatorni enzimi, PC-1, DPP IV, 5'-nukleotidaza, dijabetes, insulinska rezistencija*