REVIEW PAPER

# THE ROLE OF GALECTIN 3 IN THE PATHOGENESIS OF DIABETES MELLITUS: FOCUS ON β-CELL FUNCTION AND SURVIVAL

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## ABSTRACT

*Galectin 3 is a lectin expressed in many tissues with a significant biological role in physiological and pathological processes. Our review aims to sublimate the effects of galectin 3 on the β-cells function and survival. Data about the effect of galectin 3 on β-cells are scarce and contradictory. Several studies have shown that reduced activity of the galectin 3 gene reduces the risk of developing type 1 diabetes in an experimental model of diabetes in galectin 3 deficient mice. On the other side, in an experimental model of type 1 diabetes with mice with selectively enhanced expression of galectin 3 in β-cells, was shown that increased expression of this lectin has a protective role. Unlike type 1 diabetes where the autoimmune process plays a dominant role in pathogenesis, the pathogenesis of type 2 diabetes is multifactorial. One of the main factors which contribute to type 2 diabetes, the insulin resistance, is related to the concentration of soluble galectin 3. The effect of galectin 3 is very important for β-cell function. When a harmful factor acts on a β-cell, its intracellular concentration increases to preserve the function of β-cells and prevent their apoptosis, by blocking the internal path of apoptosis. However, excessive accumulation of galectin 3 inside the cell leads to its secretion, which encourages tissue inflammation. Based on all the above, galectin 3 has a double effect on β-cells.*

***Keywords***: *Galectin 3, type 1 diabetes mellitus, type 2 diabetes mellitus.*

## INTRODUCTION

Galectins are carbohydrate-binding proteins that are involved in many physiological functions (1). Galectin 3 is a monomer with two functional domains (2-5). So far, it is unique molecule in a lectins family with an extra-long and flexible N-terminal domain composed of 100 to 150 amino acid residues, while lacking a charged or large side chain of hydrophobic residues (3, 4). The N-terminal domain contains sites for phosphorylation of Ser 6, Ser 12, and other determinants important for lectin secretion by a nonclassical mechanism until the second C-terminus consists of about 135 amino acid residues (6-8). This lectin acts as a receptor that binds molecules - ligands that contain poly-N acetylactosamine sequences that consist of many disaccharide units. However, it appears to have an increased affinity for binding more complex oligosaccharides (9, 10). It is a unique galectin that can form pentamer units with other molecules. It has a specific pleiotropic biological function and plays an important role in many physiological and pathological processes.

Galectin 3 is the lectin that is ubiquitously expressed in many tissues. Experiments performed on mice during embryogenesis, have shown that its expression depends on the tissues and age. It is mainly expressed on epithelial cells and myeloid cells, and also in cells of the eye, renal tissue, pancreas, salivary gland ducts, as well as intrahepatic bile ducts (11). There are numerous data on the expression and effect of galectin 3 in immune system cells and cells involved in the immune response (12-14). In some cell types, galectin 3 is not expressed, but its expression can be induced through stimulation by various stimuli (15). In cells of a human exocrine pancreas, it is quite poorly expressed. Galectin 3 is mostly present in ductal cells (in about 50% expression is high) while some of the acinar cells shows low expression in nuclei (16).

### Pancreatic β-cells

Pancreatic β-cells are very important for normal metabolism as the only cells that produce insulin. As such, many conditions in the body require their increased involvement. Apoptosis is the dominant type of β-cell damage in the development of type 1 (T1DM) and type 2 diabetes mellitus (T2DM) (17-18). When the damage of β-cells is caused by metabolic causes, the main place is occupied by activation of the intrinsic apoptosis pathway (19). On the other side, in the case of damage by immune mechanisms such as pro-inflammatory cytokines or cells, the external path of apoptosis occupies a significant place (17). Disruption of the number and function of β-cells, which is followed by a disorder of glucose metabolism, simultaneously leads to a disorder of the metabolism of other organic substances (20-22). Insulin, by inhibiting lipoprotein lipase, has a strong effect on fat breakdown (23, 24). In the absence of insulin effect in the body, a redirection of metabolism to fats represents the dominant process (25, 26).

### Galectin 3 in type 1 diabetes mellitus

Data about the effect of galectin 3 on β-cells are scarce and contradictory. The onset of T1DM is associated with the development of an autoimmune process (27, 28). During this process, the immune system cells can directly cause β-cell damage or by secreting pro-inflammatory cytokines (29). The effect of galectin 3 in the β-cells pathophysiology on human cells was investigated *in vitro*. *Karlsen* et al. examined the survival of human cells after treatment with harmful immune factors. They showed that this molecule is a naturally up-regulated defense protein of β-cells, whose increase occurs upon stimulation by immune factors associated with T1DM. But, in the end, they concluded that although its enhanced production occurs, it is not sufficient to prevent β-cell damage from the effects of multiple pro-inflammatory cytokines (TNF-$\alpha$, INF-$\gamma$, and IL-1$\beta$) (30). On the other side, *Saxida* et al. investigated the effects of complete galectin 3 deficiency in β-cells *in vitro,* by treating the pancreatic islets with the cocktail of pro-inflammatory cytokines (TNF-$\alpha$, INF-$\gamma$, and IL-1$\beta$). They showed that galectin 3 deficiency promotes β-cell survival and function. Examining the expression of molecules associated with apoptosis showed that galectin 3 ablation affects the expression of the major components of the mitochondrial apoptotic pathway (internal) (31). *Mensah-Brown* et al. have shown that reduction in galectin 3 gene activity results in reduced susceptibility to T1DM development in the experimental model induced by the use of multiple low dose streptozotocin (MLD-STZ) in galectin 3 deficient mice (32). The results of our study, in mice with selective galectin 3 overexpression in β-cells, showed that enhanced galectin 3 expressions in β-cells in the MLD-STZ T1DM model had protective role. We have shown that increased expression of galectin 3 in β-cells leads to amelioration of metabolic parameters, accompanied by less severe inflammation of pancreatic islets and decreased number of pro-inflammatory cells in the islets and pancreatic lymph nodes (33). *Radosavljevic* et al. have summarized the effects of galectin 3 during autoimmunity. They showed that galectin 3 is involved in immune mediated β-cell damage and is required for diabetogenesis in the MLD-STZ model. This effect is achieved by promoting the expression of IFN-γ, TNF-$\alpha$, IL-17 and iNOS in immune and accessory effectors cells (34). *Sano* et al. have shown that the presence of galectin 3 is very important for macrophage function. In the absence of this molecule, macrophages are not effective in eliminating intracellular and extracellular pathogens (35). *Radosavljevic* et al. have shown that galectin 3 can have different effects depending on the tissue in which it is located and its location (36).

### Galectin 3 in type 2 diabetes mellitus

Unlike the T1DM pathogenesis where the autoimmune process plays a dominant role, the pathogenesis of T2DM is multifactorial (37). A couple of major factors in the development of this type of diabetes are associated with the

extracellular and soluble galectin 3 concentration. One of the major factors which contribute to β-cell damage and the development of T2DM is insulin resistance (IR). *Li* et al. showed the effect of soluble galectin 3 on the development of IR in a mouse model. They have shown that an increase in soluble galectin 3 leads to a disorder of the Glut 4 receptor expression on peripheral tissues. Decreased expression of this receptor due to interactions with soluble galectin 3 leads to increased IR. The same authors also showed that the administration of galectin 3 inhibitors improves insulin sensitivity (38). Contrary, *Pejnovic* et al. showed that galectin 3 deficient mice had a higher degree of IR compared to the control group (39). An interesting study showed that the application of piperine on C57BL/6 mice protects β-cells from dysfunction. This effect has been shown with significantly reduced levels of serum lipopolysaccharide, IL-1β, and galectin 3. Suppression of the presence of M1-like macrophages in epididymal adipose tissues and islets was also observed. In other words, piperine significantly reduces the pro-inflammatory polarization of macrophages and β-cell damage in the pancreatic islets (40). A several human studies showed that an increase in soluble galectin 3 is accompanied by an increase in IR while the results of few others say the opposite. Clinical studies have shown that patients with high serum galectin 3 values are at increased risk for obesity, prediabetes, T2DM, and chronic complications (41-43). On the other side, some clinical studies indicate that galectin 3 is negatively associated with insulinemia and insulin resistance index values and has a protective role in T2DM (44). At the same time, with the appearance of IR, metainflammation develops in adipose tissue and pancreatic islets (45). New condition is accompanied by increased production of pro-inflammatory cytokines, and also by the influx of pro-inflammatory cells. *Pejnovic* et al. showed that galectin 3 is a regulator of metaflammation in adipose tissue and pancreatic islets by examining the role of this molecule in galectin 3 deficient mice (46). Our previous results show that extracellular galectin 3 acts as an alarm. In conditions of increased concentration in the cell, galectin 3 secretion occurs. In secreted form, galectin 3 has paracrine effect on the surrounding cells, and increases the influx of inflammatory cells and inflammation (47). *Pejnovic* et al. examined the development of inflammation in adipose tissue and pancreatic islets in galectin 3 deficient mice on a high fat diet. Their results clearly showed protective roles in obesity induced inflammation and diabetes. They showed that galectin 3 deficiency accelerates the development of obesity and increases the degree of inflammation of adipose tissue and islets (39). A state of metainflammation is accompanied by increased production of pro-inflammatory cytokines, and increased influx of pro-inflammatory cells (48, 45). Some of the cytokines (IL-1$\beta$, IFN-$\gamma$, and TNF-$\alpha$) can directly impair β-cell function, while at the same time, others (IL-1 and IL-6) can increase existing inflammation. A significant place in β-cell damage occupies an interaction of macrophages and β-cells, via galectin 3 and TLR-4 receptors on both types of cells (49, 46). *Caberoy* et al. have demonstrated that the expression of galectin 3 on apoptotic cells or cellular debris is an "eat-me" signal which stimulates phagocytosis of these cells. (50) *Cucak* et al. showed that pro-inflammatory M1-like macrophages invade diabetic islets in type 2 diabetes. They even shown that innate immunity has a significant place, with changes from the original pro-inflammatory phenotype to the profibrotic phenotype, which supports the concept that T2D represent an inflammatory disease (51).

An interesting study is coming from *Hu* et al. They showed that membrane and extracellular galectin 3 interaction with immune cells, lead to β-cell damage. By using pectin, galectin 3 binding molecule that prevents interacting of galectin 3 with other molecules/cells, they have shown the reduced ROS production in β-cells and reduced inflammation in islets (52). Increased concentration of pro-inflammatory cytokines in adipose tissue at the same time reduces the production of adipokines that promote β-cell function (53).

On the other side, the expression of galectin 3 in the β-cells has a major effect. Under conditions of IR and compensatory hyperinsulinemia, there is increased stress on β-cells. Increased insulin production is accompanied by the increased mitochondrial burden which is followed by increased production of reactive oxygen species (ROS) (54-56). In addition to increased β-cell engagement, hyperglycemia *per se* can lead to the accumulation of glycation end products (increased advanced glycation end products (AGE) generation) and redox imbalance. (57) In the state of increased stress and ROS formation, various mechanisms are activated in β-cells to prevent mitochondrial damage and cell death (58). Studies which examined the effect of galectin 3 on cell damage due to increased AGE production have indicated that galectin 3 is operating *in vivo* as an AGE receptor which protect against AGE dependent tissue injury (59, 60). Our *in vitro* results showed that enhanced intracellular galectin 3 expression was associated with the prooxidant state (47).

The function of the endoplasmic reticulum (ER) occupies a significant place in the normal functioning of β-cells (61). In addition to insulin synthesis, also plays an important role as a regulator of intracellular calcium concentration, which is especially important during the first phase of insulin secretion (62, 63). In chronic conditions of β-cell exposure to various nutritional factors or hyperinsulinemia, increased ROS production is accompanied by more pronounced ER stress (64-66). Simultaneously, high concentrations of ROS can induce DNA damage and alter mitochondrial membrane potential (67). In conditions of reduced ATP production, the influx of extracellular calcium into β-cells is also reduced (68). In order to maintain insulin secretion, in the new conditions, ER becomes a source of intracellular calcium, which is accompanied by a reduced concentration of calcium in the ER. Decreased calcium concentrations in the ER lead to disturbances in preproinsulin processing as well as transport to the Golgi complex (68). The net effect of the disorder in the ER will be strain on the ability of the β-cell to manufacture process and store sufficient insulin to cope with demand and to appropriately regulate insulin secretion. Experimental studies showed that impaired mitochondria dysfunction increased ER stress proteins and induced

apoptosis of mouse pancreatic β-cells (69). Increased concentration of intracellular galectin 3, in states of metabolic stress, stabilizes the mitochondrial membrane thereby allowing increased ATP production. Enough ATP allows the influx of extracellular calcium and prevents further increase of ER stress and ultimately allows longer survival of β-cells.

Finally, one of the last mechanisms that lead to β-cell damage is lipotoxicity (70-73). Lipotoxicity causes damage by two ways. First, in high-fat diets, blood free fatty acids act via TLR-4 receptor on β-cells (damage associated molecular patterns), which transmits signals inside the cell. On the other side, the accumulation of fat particles in β-cells can directly lead to their damage and disorders in insulin secretion (74, 71). Although most studies agree that galectin 3 is a marker of inflammation and fibrosis, many experimental studies indicate that increased expression of this molecule may be part of the adaptive response to tissue injury. The main goal of this response is to prevent the transition of the inflammatory process to a chronic course (75).

The effect of galectin 3 is very important for the function and survival of β-cells. In conditions when a harmful factor acts on a β-cell, an increased concentration of intracellular galectin 3 occurs. This increment occurs to preserve the function of β-cells and prevent apoptosis. The antiapoptotic effect of intracellular galectin 3 is achieved by suppressing the internal path of apoptosis. However, excessive accumulation of galectin 3 inside the cell leads to its secretion. Secretion starts when the intracellular calcium concentration increases and when the galectin 3 producing cell tends toward apoptosis due to significant ROS production. Secreted galectin 3 then attracts pro-inflammatory cells and promotes tissue inflammation. Immune cells effect on the β-cell is dominantly expressed via an external path of apoptosis in which galectin 3 does not play important role. When the concentration of galectin 3 rises in the blood, it further increases the severity of IR.

## CONCLUSION

Based on all the above, we concluded that galectin 3 has a dual effect on β-cells. Intracellular galectin 3 protects β-cells by silencing the internal pathway of apoptosis while extracellular promotes insulin resistance and inflammation of the pancreatic islets.

**Table 1.** Summary effects of galectin 3 on β-cell

| **Effect of galectin 3 on β-cell function and survival** | |
|---|---|
| **Protective in T1 diabetes/T2 diabetes** | |
| **Study** | **Type** |
| ***Karlsen* et al. (2006)** | ***in vitro*** |
| ***Jovicic* et al. (2021)** | **on galectin 3 OE mice** |
| ***Pejnovic* et al. (2013)** | **on galectin 3 KO mice** |
| ***Pejnovic* et al. (2013)** | **on galectin 3 KO mice** |
| **Harmful in T1 diabetes/T2 diabetes** | |
| **Study** | **Type** |
| ***Saksida* et al. (2013)** | ***in vitro*** |
| ***Mensah-Brown* et al. (2009)** | **on galectin 3 KO mice** |
| ***Li* et al. (2016)** | **on Galectin 3 KO and WT C57BL/6 mice** |
| ***Yuan* et al. (2021)** | **on C57BL/6 mice** |
| ***Petrovic* et al. (2020)** | **on galectin 3 OE mice** |
| ***Hu* et al. (2020)** | ***in vitro*** |
| ***Caberoy* et al. (2012)** | ***in vitro*** |
| ***Weigert* et al. (2010)** | **on humans** |
| ***Yilmaz* et al. (2015)** | **on humans** |
| ***Jin* et al. (2013)** | **on humans** |


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## CONFLICTS OF INTEREST

The authors declare no financial or commercial conflict of interest.

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