THE ROLE OF MAST CELLS IN TYPE I DIABETES MELLITUS

Serghei Covanţev, Dumitru Ciolac
(Scientific Advisor – MD, PhD, Associate Professor Lilian Şaptefraţi)
Department of Histology, Cytology and Embryology, USMF "Nicolae Testemiţanu"

Summary

The incidence of type I diabetes mellitus is rising 3-5% per year. The general prevalence of this disease ranges from 1.6 - 30.9% depending on the country. The modern field of diabetology proposes different mechanisms for development of the disorder. Still insulitis remains the main cause, ranging from 54 - 89%, confirming the autoimmune genesis of type I diabetes. Mast cells have a wide range of functions in the connective tissue that raise many questions about their putative role in type I diabetes. In this article is presented a review of studies which show mast cells involvement in the pathophysiology of diabetes.

Rezumat
Rolui celulelor mastocitare în diabetul zaharat de tip 1

Incidenţa diabetului zaharat de tip I creştere cu 3-5% pe an. Prevalenţa generală a acestei maladii variază intre 1.6 - 30.9%, în dependenţă de ţară. Domeniul al diabetologiei contemporan propune diferite mecanisme în dezvoltarea acestei maladii. Totuşi insulită rămâne a fi cauza principală, variind intre 54 - 89%, confirmînd geneza autoimună a diabetului zaharat. Mastocitele au o gamă vastă de funcţii în ţesutul conjunctiv, care ridică multe întrebări privind rolul lor posibil în fiziopatologia diabetului zaharat de tip I. Articol prezintă revizuire de studii care leagă celulele mastocitare, cu fiziopatologia diabetului zaharat.

Introduction

Recent studies show the increase of morbidity of type I diabetes (T1D) worldwide. The prevalence of this disease was 2,8% in 2000. It is estimated that in 2030 it may already be 4,4%, thus increasing the diabetic „population" between 171 and 366 millions worldwide. The general prevelence of T1D can range from 1.6-30.9% depending on the country [21, 22, 24].

The last few centuries marked a great progress in the field of diabetology. It also has showed the complex nature of the disorder. T1D usually occurs in young people. Insulitis is found in the majority of cases, ranging from 54-89%, which makes T1D mostly an autoimmune disease [20]. This disease causes destruction of the pancreatic beta cells, leading to insulin deficiency. Over the past years a lot of new data was discovered about the different aspects of the disease, revealing its complexity. Still there is no doubt that prevention of this disease is essential [19].

Mast cells are currently in the period of their «renaissance» with new and new discoveries of their role in different pathological conditions. But still their main role is local homeostasis regulation. Mast cells are present anywhere where there is at least a small layer of connective tissue. And the pancreas is not an exception. This leads to the hypothesis that they may be involved in the autoimmune disorders linked to T1D.

More evidence point their role in different autoimmune disorders [2, 15]. Researchers are currently working on so-called "antigen-specific therapies," which will correct the defect in the immune system, as well as the possibility of using short-term suppression of the immune system that will reduce the destruction of beta cells of the islets of Langerhans. There are suggestions that lymphocytes are not the only participants in the development of diabetes and now stand along with mast cells, neutrophils and natural killer cells [1].

Istlet pathomorphology in T1D

Several factors are involved in the pathogenesis of T1D such as genetic, environmental, dietary etc. Currently T1D is thought to be due to autoimmune destruction of β-cells. An autoimmune etiology was first proposed after detection of islet autoantibodies in the serum of

diabetic patients. Histologicaly T1D presents as lymphocyte infiltration of the pancreatic islets. The reason of this infiltration is still unknown and a number of theories were proposed in the last years. New data involving animal experimental models shows that T1D can develop due to a number of underlying conditions such as viral infection, thymus and pancreatic lymph nodes dysfunction etc [4, 20].

B-cells also are involved in the pathogenesis of T1D by secreting anti-islet antibodies that activate CD4$^+$ cells. B-cell depletion results in 60% chance protection from T1D in mice. [7, 18]

In 1965 W. Gepts classified islet pathology into 3 types. Type I islets are characterized by irregular outline between the β-cells and acinar cells. The islets had a reduced size and there was no evidence of degranulation.

Type II islets are on the other hand are larger in size with bigger nuclei unlike type I islet cells. The cytoplasm was often free of granules but they still could be found in some particular cells.

Type III islet cells are considered normal and are rarely found in diabetic patients. Their degranulation and synthetic activity is normal.

Another important feature is that β-cell destruction is a more localized process thus for a period of time there can be an area with type III as well as type I cells [9].

On the other hand β-cells don't undergo complete destruction. Hillary A. Keenan et al., 2010 studied a cohort of patients with a disease duration of 50 years. 9 postmortem examination showed that even after 50 years of T1D β-cells can still be found in the islets. This gives a possibility to reverse T1D even after a long duration of the disease [13].

Mast cell receptors, activation and contradictory role in T1D

Mast cells are present near the pancreatic ducts, close to endothelial cells. So they are located relatively close to the pancreatic islets. Recent publications present contradictory data. Some researchers indicate their role in the protection against diabetes, others the key role in its pathogenesis. This can be explained by a model in which the activity of mast cell depends on the substance which is present in high amounts in the tissues [6].

During the last years several new receptors were identidied on the surface of mast cells. The substances that bind with their surface receptors largely define mast cell actvity [7, 14, 15, 16, 17].

Furthermore depending on the activation molecules mast cells can react with other cells through cross-talk, such as dendritic cells, neutrophils, CD4+, CD8+ and B cells. Thus activating or inhibiting their activity. Current data indicates that many autoimmune diseases involve the CD4+ cells [3].

Mast cells can activate Th17 by means of IL-6 or transforming growth factor b (TGF-b) or inhibit them through Th2 cells with IL-4. Th17 cells are a type of T helper cells that prodeuce interleukin 17 (IL-17). Curent data shows that increased activation of this type of cells leads to several autoimmune conditions among which is juvinile diabetes.

Or mast cells can activate dendritic cells through interleukin 4 (IL-4), prostoglandin D2 (PGD2) and histamine which can ether activate Th1 or Th2 cells. Dendritic cells are also involved in several autoimmune diseases.

By releasung TGF-b mast cells can activate Treg cells which can inhibit Th17 and Th1.

Through programmed cell death 1 ligand (PD-L1) mast cells inhibit both CD8+ and CD4+ cells.

Also by releasing proteolitic enzymes (chymase, tryptase, cathepsin G, carboxypeptidase A) they can damage b-cells without cell-cell interaction [6].

Table 1

List of several mast cell receptors, substances that bind to them and their effects

Receptor	Ligand	Function
Adenosine receptors (A2A, A2B, A3)	Adenosine	Effects ranging from degranulation to inhibition
B2-Adrenoreceptor	Adrenaline	Inhibition of degranulation
C3a receptor C5a receptor	C3a C5a	Degranulation, chemotaxis, chemokine secretion
Cannabinoid CB2 receptor	2-Arachidonoyl-glycerol, anandamide	Supression of mast cell activity
CD200 receptor	CD200	Inhbitory action
CD300a	Eosinphil granule proteins	Histamine secretion
Chemokine receptors	Chemokines	Migration, degranulation
Leukotriene receptors 1 & 2	Leukotrienes	Induction of cytokine generation and proliferation
Estrogene receptor	Estrogenes	Mediator release
FcεRI, FcγRI, FcγRIIA	IgE, IgG	Stimulation of mast cell activity
FcγRIIB	IgG	Inhibition of mast cell activity
Histamine receptors (H1, H2, H3, H4)	Histamine	H1, H2-calcium mobilization H3-autoregulation of histamine release H4-chemotaxis and calcium mobilization
5-HTR	Serotonin	Cell migration
IR	Insulin	Increases mast cell activity
LIRs, KIR	HLA	Inhibition of mast cell activity
Prostaglandin E receptors (EP2, EP3, EP4)	Prostaglandin E	EP2 - inhibition of mast cell EP3, EP4 - activation
Purinoreceptors	ADP, ATP, UTP	Stimulation of mast cells
Siglec 2, 3, 5, 6, 7, 8, 10, 11	Sialic acid	Inhibition of mast cell activity
Vitamin D receptor	Vitamin D	Mast cell development

Experementaly prooven effects of mast cells include activation, maturation and recritment of dendritic cells and neutrophils. They cause proliferation and differentiation of B cells. Can support and activate Treg cells. Also they can act as antigen presenting cell and thus co-stimulating T-cells [2].

The mechanism of activation and cells that are activated largely define the final result. On one hand mast cells can promote inflamatory processes and on other hand they supress them.

The positive and negative roles of mast cells in T1D

Several studies indicate that mast cells can slow down or promote the process of beta cell destruction.

A.L. Christy and M.A. Brown, 2012 have shown that tumor necrotic factor a (TNFa), TGF-b regulate T cell tolerance to autoantigens in some cases of T1D. Mast cells inhibit Th1, Th17 through Treg cells, thus slowing down the inflammatory response. Secretion of PD-L1 can supress CD4+, CD8+ [6].

Experimental models demonstrate that continuous administration of anti-FcεR1 antibodies in non obese diabetic mice can lead to ~50% protection from diabetes for a period of time. This is due to large amount of IL-4 circulation released by mast cells and basophils. The total number of β-islet cells was also increased compared with the control group [11].

R. Geoffrey et al., 2006 described significant delay of T1D in mice using cromolyn as a mast cell "stabilizer", which indicates the role of these cells in the early stages of the disease [8].

It is important to mention that excessive amounts of corticosteroids in blood not only inhibits insulin synthesis but also decreases the amount of mast cells, as well as the level of IL-3 and IgE. Bilateral adrenalectomy or corticosteroid receptor blockage increases the quantity and functional potential of mast cells. Insulin and insulin growth factor 1 (IGF-1) increases mast cell degranulation and affects their cytoskeleton [20].

Several authors demonstrated decrease in sodium channels by 50% as well as the activity of mast cells in tissues with decreased level of insulin [7]. Several studies show decrease of immune responses in diabetics suffering of asthma which can also be explained by decrease of mast cell activity in diabetes [5, 10].

M. Kaldunski et al., 2010 used IL-1 receptor antagonist and found that administration of IL-1Ra to pre-diabetic mice delayed the onset of the disease [12].

Conclusion

Current data indicates the involvement of mast cells in the development of T1D. But this role is determined by the increase or decreased amount of certain chemicals that affect these cells. Proper use of this knowledge can help specialists delay the manifestations of T1D in the population.

Another possibility is the use of certain substances in order to inactivate certain receptors on mast cell surface. Receptor inactivation can inhibit certain mast cell functions that have a role in T1D development.

Also certain drugs can be used in order to influence on mast cell inhibitory action thus affecting multiple cells of the immune system on different levels.

Early diagnosis of elevation in pro-inflammatory markers in blood (for example interleukins such as IL-1b) can indicate the early onset of the disease, thus there is a possibility to identify the risk group for diabetes more accurately than it is now.

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THE ROLE OF MAST CELLS IN INFLAMMATORY REACTION IN BURN INJURY AND POSTBURN REGENERATION

Serghei Covanţev, Dumitru Ciolac
(Scientific Advisor – Assistant Professor Tatiana Globa)
Department of Histology, Cytology and Embryology, USMF "Nicolae Testemiţanu"

Summary

Each year, approximately 11 million patients are hospitalized due to burn injuries. Mortality from burns ranges from 1.4% to 18% (Europe). At the same time burn injuries can lead to disability, and full recovery is often impossible. Mast cells can play an important role in burn injuries and regeneration. For a long time these cells had been neglected by scientists. Only recently new data has started to appear about their structure and functional significance in the local homeostasis. The list of substances synthesized by mast cells has significantly expanded, and so has the list of cells which they can influence. A review of studies on mast cells regarding their role in burn injury and its subsequent regeneration is presented in this article.