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http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **19**(1):67-72
doi: 10.2478/v10255-012-0009-1

PATHOGENESIS OF TYPE 1 DIABETES MELLITUS: A BRIEF OVERVIEW

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received: December 01, 2011 *accepted*: February 2, 2012

available online: March 30, 2012

Abstract

Before the discovery of insulin, type 1 diabetes mellitus (DM) was a disease with acute evolution, leading to death shortly after diagnosis. During the first years of insulin therapy, the medical world was optimistic, even enthusiastic, considering that the therapeutic solution for the malady was found. Unfortunately this was only an illusion, because the patients started to develop chronic complications that shortened their lifespan and impaired their quality of life. In other words, insulin therapy transformed type 1 DM into a chronic disease. The prevention or the delay of the onset of hyperglycemia emerged as a new solution for the patients and, consequently, the understanding of the pathogenesis of the disease (a prerequisite for developing efficient preventive methods) became a priority for all the diabetologists involved in research. Almost 40 years have passed since the autoimmune theory regarding the pathogenesis of type 1 DM was imagined but, despite the tremendous research performed in this field since then, the prevention could not be obtained. The aim of this paper is to present the most important theoretic notions regarding the mechanisms that underlie the development of type 1 DM, in the way they are understood today.

key words: *type 1 diabetes mellitus, pathogenesis, autoimmunity, genetic*

Type 1 diabetes mellitus (T1DM) is a relative common disease, currently affecting about 0.3% of the population in developed countries. It has an incidence that increases with approximately 3% every year and produces sometimes disabling micro- and macrovascular complications. Thus, T1DM represents a great financial burden to the society, but even more a burden to the individual and his or her family.

The disease recognizes two major subtypes: 1A (autoimmune) and 1B (idiopathic). Once considered a disease of acute onset, it is now generally accepted that 1A subtype is a genetically determined chronic immune-mediated disorder that leads to selective loss of pancreatic insulin-secreting β-cells. It starts with a long subclinical prodromal phase that lasts for years and is associated with several immunologic

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abnormalities. Some of these can be used to detect those individuals that eventually will develop T1DM.

Understanding the etiology and pathogenesis of human T1DM is a difficult task. The main issue is that we are probably dealing with a localized, slowly progressive, inflammatory reaction, that is mostly confined to the pancreatic islets and draining lymph nodes. Since the human pancreas is located retro-peritoneally, samples or live cells cannot be obtained easily. Furthermore, non-invasive imaging does not have the required resolution to allow precise analysis of the cellular immunological process. Thus, our knowledge of the disease in humans is largely based on the assumption that animal models allow us to draw parallels.

The classic point of view regarding T1DM pathogenesis was that, in genetically predisposed individuals, some environmental factors may trigger an autoimmune process that leads to β-cell destruction. In the last 4 decades, a dramatic increase in the biochemical identification of islet autoantigens and in the definition of alleles of genes associated with diabetes susceptibility was registered. Nowadays, one considers that genes and environmental factors may have deleterious or favorable effects and, consequently, the immune equilibrium is directed towards aggression or protection.

It is the time to recapitulate here the main knowledge we have about the pathogenesis of autoimmune T1DM.

Genetic and environmental triggers. The genetics of T1DM are quite well understood. It is clear at this point that multiple genes can have predisposing, as well as protective effects, resulting in a complex interaction. Overall contribution of genetic factors will not explain the etiology of disease alone, since there is a significant discordance in monozygotic twins [1, 2]. Other environmental factors are therefore important, and many potential candidates were under evaluation; among them dietary factors, cow's milk in young infants, viral infections and psychological stress [3]. Viruses have been shown to influence the diabetic process in a positive or negative way in animal models [4]. In humans, no association has been proven, although Coxsackie and rotaviruses have been reported to precede autoantibody seroconversion in young infants [5]. Viruses could favor disease occurrence through mimicry, enhanced local inflammation or bystander activation. They could also exert protective effects by inducing apoptosis of aggressive lymphocytes and immune modulation. Consequently, it is well possible that viruses, similar to genes, contribute to T1DM pathogenesis in a multifactorial way [6].

Autoantibodies. Autoantibodies to islet antigens can be detected in serum samples from pre-diabetic individuals and newly diagnosed cases [7, 8]. They predict the risk to develop disease and antibodies to multiple β-cell antigens (insulin, GAD65, IA-2, ZnT8 etc.) are associated with a very high likelihood of clinical T1DM. However, it is still controversial whether such autoantibodies play a pathogenetic role. Plasmapheresis in humans only temporarily clears islet-antibodies from the circulation and no effect on T1DM development was observed after the procedure [9, 10]. Studies in the NOD mouse model suggest a role for maternal antibodies in initiating diabetes development in offspring [11]. This is less clear in humans, because no differentiation between maternal antibodies

generated as a consequence of insulin therapy and islet-autoimmunity was possible. However, no direct association has been established at this point and, even more, offspring from diabetic fathers carry a higher diabetes risk than those from diabetic mothers. Future investigations, focusing on the correlation between antibody-isotypes and avidity, on one side, and disease risk, on the other, will probably clarify their possible pathogenetic role, in particular in young children [12].

T lymphocytes. Predominantly based on animal experimentation in the NOD mouse or transgenic models, T1DM is thought to be a T cell mediated autoimmune disorder. However, one has to acknowledge that infiltrates found in human islets are less T-cell rich than those present in mice. In contrast to autoantibodies, T cells, as well as clones with specificity for islet antigens, can transfer disease in animal models. Comparable studies are impossible in humans and that's why no definite proof in respect to the importance of T lymphocytes has been obtained. However, indirect proof can be attributed to temporary success of systemic immunosuppressive regimens such as antibodies to CD4 or CD3 and cyclosporine A [13]. Generally, autoreactive T cells are difficult to detect, in particular in human peripheral blood. At this point one can therefore assume that numbers of autoreactive lymphocytes in T1DM are low and that they are mostly localized in the pancreas and draining lymph nodes [14]. Better tracking reagents might elucidate their pathogenetic roles [15]. Current evidence from animal models indicates that autoreactive lymphocytes can have destructive or regulatory effector functions, depending on which cytokines they produce [14]. One issue that is emerging is to determine which factors or cells provide the continuous drive for autoreactive T cells during a chronic autoimmune process that can take place over many years. Experimental studies in animal models have shown that autoreactive T cells can easily be suppressed and that local inflammation might be required to initiate and maintain autoaggression [16]. It is therefore important to consider the role for antigen presenting cells (APC) in T1DM.

Antigen presenting cells. Due to the relative paucity of lymphocytes, human islet infiltrates are exhibiting a high number of monocytes and possibly other APC. Activated APC are detectable early in human pancreas. In animal models, they are of critical importance for driving the local inflammatory process and providing continued opportunity for autoreactive T cells to become activated. Once destruction of some islet cells has occurred, it is supposed that local APC will increasingly present β-cell antigens. This leads to antigenic and epitope spreading, if non-tolerant T cells to the respective antigen are available in the periphery. Furthermore, activated APC might be required for the arrival of autoreactive lymphocytes, without which these would not be capable of causing chronic inflammation and disease. On the other hand, however, one must acknowledge that NOD mice as well as diabetic patients have distinct defects in APC activation and stimulatory capacity. In conclusion, the precise role of APC is unclear at this point.

Systemic defect in immune regulation (dysregulation). There is relatively good evidence from human studies that natural killer (NK) T cell activity, APC function as well as generation of CD25+ regulatory lymphocytes are all reduced in human diabetic

patients [17]. This finding, coupled with strong evidence from animal models that enhancing NK T cell activity [18], systemic infections leading to immune activation or transfer of CD25+ cells [17] can prevent T1DM, makes generalized immune dysregulation a likely underlying cause for T1DM. Genetic factors and environmental influences might all be able to enhance or alleviate this systemic dysregulation. It is intriguing that most defects that have been found constitute a lack of certain immune functions including generation of molecules such as interferons by NK T cells that are known to be detrimental to islets. However, lack of NK T cell activity also results in less interleukin (IL)-4 production and, consequently, lower degrees of APC activation, that might result in lower levels of CD25+ or T helper 2-like regulatory cells than needed to maintain a healthy immune equilibrium. Therapeutically, this situation might be exploited, but one will have to act with caution, because any type of systemic correction will affect other immune functions, such as host defense.

A hypothesis for T1DM pathogenesis. A primary requirement for the development of islet autoimmunity is the presence of non-tolerant lymphocytes in the peripheral lymphoid organs that bear T cell receptors that can react with islet antigens. This is not an uncommon occurrence, because thymic negative selection is not complete [19]. This situation does normally not pose any problems and will not lead to autoimmunity, unless these cells become activated and gain access to the target organ. It is likely that local (intrapancreatic) events are more likely than systemic events to trigger T1DM, because systemic activation of autoreactive lymphocytes requires large numbers of activated cells that is difficult to be generated to a sufficient extent in the periphery by molecular mimicry or bystander effects [20]. As a possible local precipitator, viral infections, APC dysfunction, or even maternal antibodies could all play a role. Probably all of the above occur in conjunction with genetic predisposition. Once a sufficient number of APC, that drive autoreactive lymphocytes, has been reached in islets and draining lymph nodes, development of T1DM is on its way. As islet destruction progresses, more antigens will become targeted, reflected in increased levels and varieties of islet autoantibodies. Not all autoreactive lymphocytes have detrimental effector functions. Certain cytokines, such as IL-4 or IL-10, can have positive effects [14], if expressed at the right level and time prior to massive islet loss. This can be therapeutically exploited and, possibly, the ideal intervention would be a combination of both: augmentation of regulatory responses and inhibition of aggressive anti-islet activities. This could be achieved by combining systemic modulators such as anti-CD3 [21] or vitamin D3 analogs with islet-antigen specific DNA vaccines that induce regulatory lymphocytes [22]. Regardless of the etiology, the crucial effector pathways in islet destruction are known. Cytotoxic T cells, type 2 interferon [23], tumor necrosis factor α, IL-1β and nitric oxide generation are all detrimental to β-cells [24]. These can be produced by various effector lymphocytes, including APC and B cells, explaining the redundancy of the mechanism. These considerations make effective late interventions harder to achieve. However, one must not forget that successful islet destruction will rely on a critical mass of inflammation. Thus, "resetting" the system

can break the vicious cycle (for example by anti-CD3 or similar agents). Long term tolerance, however, should be maintained in an antigen specific way, in order to avoid prolonged systemic immunosuppression [22, 25].

Despite considerable progress over recent years, the autoimmune process underlying T1DM is still poorly understood. The prediction of the disease, based on autoantibody positivity, is far from being perfect [26, 27]. This has made it difficult to design strategies to target the process underlying immune-mediated β-cell destruction. Potential interventions strategies include antigen based therapies (insulin or insulin fragments), monoclonal antibodies, cytokine-based therapies and other strategies. One can hope that, in the future, better understanding of the pathogenic process will make possible the development of effective interventions to prevent T1DM [28].

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