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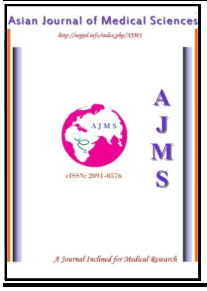

Impact of Lymphocyte Apoptosis in Diabetes Mellitus

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Abstract

Diabetes mellitus is a metabolic disorder. It is the most common cause of blindness, kidney failure, and amputations in adults and a leading cause of heart disease and stroke. These patients are more prone to infection which shows that there is suppressed cell mediated immunity during diabetes progression. Lymphocytes play a crucial role in maintenance of cellular & humoral immunity both and its development requires cellular selection to remove potentially auto reactive cells via apoptosis. Apoptosis of lymphocyte clones play a pivotal role in purging the body of dangerous lymphocytes to maintain the development and regulation of the immune system. Indeed, inefficient elimination of lymphocytes can contribute in the pathogenesis of autoimmune diseases like insulin dependent diabetes mellitus. Several clinical and experimental studies have revealed that uncontrolled diabetes leads to lymphocyte death which enhances susceptibility towards infections and creates a permissive environment for bacterial growth. The aim of this article is to review the findings that the high incidence of infection in poorly controlled diabetic states may be positively correlated with an increased proportion of apoptotic lymphocytes.

Keywords: Lymphocyte; Infection; Programmed cell death; Autoantigens; Immunity

1. Introduction

Diabetes mellitus is a chronic, debilitating and often fatal disease that affects all races in the world.[1] It is the most common cause of blindness, kidney failure and amputations in adults and a leading cause of heart disease and stroke. International Diabetes Federation (IDF) has estimated that there will be 285 million cases of diabetes globally by 2010. This number is expected to increase by more than 50% in the next 20 years, if preventive measures are not applied rightly. By 2030, some 438 million people are projected to succumb diabetes.[2] The two most common forms of diabetes are type 1 diabetes mellitus (T1DM), previously known as insulin-dependent diabetes mellitus (IDDM) and type 2 diabetes mellitus (T2DM), previously known as non-insulin-dependent diabetes mellitus (NIDDM). Both are caused by a combination of genetic and environmental risk factors. Diabetic individuals are at high risk of infectious diseases and often respond poorly to infections once they occur, leads to serious complications.[3] It has been well studied that lymphocytes are the main constituents of the immune system which provides defense against pathogenic micro-organisms such as viruses, bacteria, fungi and parasites. The functional regulation of lymphocytes is crucial to protect body from different immunity related abnormalities. They are precisely regulated under stringent physiological conditions to manifest proper development, homeostasis, and immunity against diseases.[4] Programmed cell death plays crucial role to regulate proper immune functioning.[5] Under normal conditions, the death of immature lymphocytes occurs due to binding of autoantigens leading to apoptosis.[6] During acute infection, the lymphocyte count increases 4 to 15 folds in comparison to normal conditions. Because the immune system cannot sustain such massive cellular burden for an extended period, the system needs a mean to eliminate unneeded activated lymphocytes once the antigenic threat is over. These unneeded activated lymphocytes are removed by programmed cell death. Programmed cell death ensures

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the proper removal of auto reactive T cells during thymic development as well as T cell homeostasis and the down regulation of immune responses against antigens in the periphery.[7] Developing lymphocytes that fail to express an antigen receptor are removed by apoptosis to ensure a functional repertoire of mature B and T cells. A defect in the deletion of these lymphocytes by apoptosis could predispose individuals to autoimmunity. Auto reactive T lymphocytes are the most important, as well as the final effector cells in autoimmune diabetes.[8-10] Few studies have revealed that, effector T cells induce apoptosis of insulin producing pancreatic ß-cells, which subsequently leads to absolute insulin deficiency clinically manifest diabetes.[11] If apoptosis malfunctions, its results may be dire and stroke damage may occur in the specific organ, however, activated lymphocytes are killed when an infection is cleared successfully.[12] Further, studies revealed that, enhanced lymphocyte apoptosis can cause immunodeficiency, on the contrary, diminutive apoptosis is responsible for autoimmune diseases (e.g. IDDM).[13] Apoptosis is regulated by the various signaling molecules; in T-cells it is initiated by the withdrawal of survival signals like Bcl-2.[14]

2. Mechanisms of Apoptosis

Apoptosis is a complex network of biochemical pathways with fine regulatory mechanisms that control a death event in a cell.[15] Few studies have explained that, it is executed through a suicide program which is common in diabetes and degenerative central nervous system disorders and the purpose is to kill unwanted host cells. It is usually used in three common situations; for development and homeostasis, defense mechanism and in aging. Apoptosis is characterized by a distinct set of morphological events involving plasma membrane blebbing, loss of cell volume, nuclear condensation, fragmentation of DNA at nucleosomal intervals and ultimate fragmentation of the cell into membrane enclosed "apoptotic bodies".[16] It can be initiated by two different but interlinked pathways: an intrinsic, mitochondria-dependent and an extrinsic, receptor induced pathway.

2.1. Intrinsic Signals

The intrinsic pathway is mediated by mitochondrial dysfunction resulting in the release of pro-apoptotic factors (cytochrome C, endo G, AIF). Cytochrome C complexes with Apaf-1 to activate procaspase 9 leading to subsequent caspase cascade followed by cell death.[17] This pathway is also controlled by the balance between pro and anti-apoptotic members of the Bcl-2 protein family.[18] Bcl-2 family is a set of cytoplasmic protein members that regulate apoptosis. The two main groups of this family, Bcl-2 and Bax proteins are functionally opposite: Bcl-2 acts to inhibit apoptosis, whereas Bax counteracts this effect.[19,20] The ratio of Bcl-2 to Bax has been hypothesized to determine cell survival or death following an apoptotic stimulus.[21]

2.2. Extrinsic Signals

The extrinsic pathway is mediated either by cell surface receptors (Fas and TNF receptor system) or by perforin and granzyme B, released from activated cytotoxic lymphocytes. Apoptosis by this pathway includes death receptor ligation, takes place either by CD95L (FasL), TNF or TNFR-related apoptosis-inducing ligand (TRAIL, also called Apo2L). This ligation leads to caspase 8 activation, procaspase 3 cleavage and subsequent cell death.[22, 23]

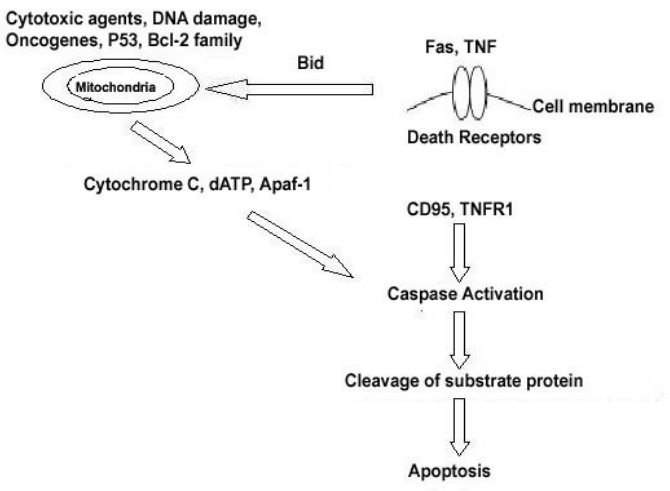

Figure -1: Outline of apoptotic events

Diabetes is associated with both enhanced TNF and fas/fas-ligand expression.[24, 25] Some other cytokines like IL- 1 or interferon-gamma may promote apoptosis, even though their receptors lack death domains, by altering pro-apoptotic gene expression or enhancing production of oxygen radicals.[26-28] Advanced glycation end-products may also promote apoptosis of critical matrix-producing cells.[29] Enhanced apoptosis of these cells is associated with diabetic complications such as retinopathy, neuropathy, nephropathy, and accelerated vasculopathy.[30-32]

2.3. Genetics of programmed cell death

Apoptosis is an essential process in embryonic development and tissue homeostasis, particularly in the prevention of disease and is sometimes quoted as necessary evil. The molecular regulation of cell survival is a fundamental determent of lymphocyte maturation, receptor repertoire selection, homeostasis and the cellular response to stressful stimuli, such as DNA damage.[33] Dysfunction in apoptosis occurs, in neurodegenerative diseases (excess apoptosis) and in autoimmune and neoplastic diseases (scanty apoptosis).[34-36] Genes play an important role in the development of diabetes mellitus and also in the lymphocytes apoptosis. Two genes are important for controlled regulation of apoptosis, Bcl-2 and p53. A family of mammalian proteins similar to Bcl-2 promotes or inhibits apoptosis.[37,38] Bcl-2 and Bcl-xL Proteins prevent apoptosis, whereas Bcl-2 associated x proteins (Bax) such as Bax, Bad, Bak and Bcl-xS promote apoptosis.[39-41] p53 is a 53-kDa nuclear phosphoprotein that binds to DNA to act as a transcription factor, and controls cell proliferation and DNA repair.[42] p53 lies at crucial intersection of apoptosis regulation through maintenance of genetic stability and proper operation of checkpoints. Proto-oncogene (cmyc) encodes a sequence specific DNA-binding protein that acts as a transcription factor and induces apoptosis in the presence of p53.

Conversely, genetic aberrations that render cells incapable of executing their suicide program results in autoimmune disorders and tumorigenesis. The CTLA-4 gene is a strong candidate gene for autoimmune diseases since it encodes for a molecule that functions as a key negative regulator of T-cell activation. CTLA-4 is critical to T-cell apoptosis.[43]

2.4. Lymphocyte impairment in diabetes

Lymphocytes are the main constituents of immune system which provides defence against the attack of pathogenic micro-organisms such as viruses, bacteria, fungi and protista. The high incidence of infection in poorly controlled diabetic states is associated with an increased proportion of lymphocytes apoptosis. An enhanced susceptibility to infections is well known to occur in poorly controlled diabetic individuals.[44] Abnormalities in the defence mechanisms of poorly controlled diabetic individuals against a variety of infectious agents have long been recognized.[45] Defects in lymphocyte apoptosis may lead to autoimmune disorders and contribute to the pathogenesis of type 1diabetes.[46] T1DM is the effect of T cell dependent autoimmune destruction of insulin producing beta cells in the pancreas islet. Involvements of T cells in the local immune reactions are confirmed by the decreased percentage of CD3 lymphocytes in the peripheral blood of patients with a high risk of T1DM.[47] Impairment in lymphocytes in the case of diabetes thus directly affects the immunity of patients which leads various complications like delayed in the wound healing process due to the increased chances of infection at the wound site.

3. Conclusion

Lymphocytes are white blood cells that tend to mitigate infections through cellular immunity. Normally, the body keeps a precise balance in which lymphocyte growth is matched by lymphocyte death. Diabetic patients, are more prone to infections, possibly due to compromised immune response.The incidence of a recognized group of rare infections are definitely high in diabetes mellitus or confined almost entirely to diabetic patients.[48] Infectious diseases, particularly tuberculosis, were a major cause of death among diabetic patients before the advent of insulin therapy.[49] Use of nanotechnology in the field of diabetes provide more accurate and timely medical information for diagnosing disease. The miniature devices that can administer treatment automatically, if required and offer new hope for the better control of diabetes mellitus.[50]

This review leads to better understanding of the importance of lymphocytes in pathophysiology of diabetes mellitus. A detailed and thorough understanding of lymphocyte cell death in diabetes is needed to be explored before start thinking of therapeutics which alter the apoptotic effector machinery for the potentiation of immunity.

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