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SHORT COMMUNICATION

Macrophages in Diabetes Mellitus: A Review on Understanding of Macrophage Function

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ABSTRACT

Diabetes mellitus (DM) causes millions of deaths all over the world. Immune system contains macrophages that play very important role in DM. Excessive secretion of different cytokines can induce the DM development. Diabetes mellitus (DM) also affect the function of macrophage. We review the important findings regarding the role of macrophage in DM. This review may emphasize future direction towards development of novel immune-modulatory therapeutic intervention.

Keywords: Diabetes mellitus, Macrophage, Macrophage Type 1, Macrophage Type 2, Cytokines, Streptozotocin, Alloxan, Diabetic Nephropathy, Diabetic Retinopathy, Beta-cell Therapy

DIABETES MELLITUS

Diabetes mellitus (DM) is a group of metabolic disease which shows hyperglycaemia caused due to impairment of insulin secretion or unresponsiveness of body's towards it or both [1]. The hyperglycaemia effects heart, kidney, eyes, blood vessel [1, 2]. Type 1 diabetes mellitus (T1D) is insulin dependent diabetes mellitus (IDDM) where body fails to produce

insulin and type 2 diabetes mellitus (T2D) is non-insulin dependent diabetes mellitus (NIDDM) where body become unresponsive to insulin.

MACROPHAGES AND DIABETES

Macrophage is one of the important immune cells that show defence mechanism against invading pathogen and also helps to remove cellular debris. Macrophage has mainly two subcategory: classically activated macrophages (CAM) or pro inflammatory macrophage which produces pro-inflammatory cytokines like tumour necrosis factor-alpha (TNF- α), interleukin-12 (IL-12), IL-1 β and alternatively activated macrophages (AAM) or anti-inflammatory macrophage which produce IL10, TGF- β (transforming growth factor- β) and low or null levels of the pro-inflammatory cytokines. They mainly synthesize IL4 & IL13 as anti-inflammatory cytokine [3, 4]. DM shows reduction of cell mediated and humoral immune response [5, 6]. During type 1 diabetes mellitus macrophage, CD4⁺ and CD8⁺ autoreactive T cell enter into the islet and TNF α , IL1 β and IL6 are increased [1, 7].

IL1 β & TNF α promotes the apoptosis of pancreatic β cell by activating NF-k β pathway and insulin production is hampered. Macrophage migration inhibitory factor (MIF) is associated with T1D. MIF influences the monocyte chemo-attractant protein (MCP1) which induces the monocyte transmigration [7, 9]. MIF inhibitor can reduce insulinitis and inflammatory response in pancreas [1, 8].

Development of diabetes occurs due to the recruitment of inflammatory monocyte that promotes inflammation and β cell destruction [1, 9].

When the majority of β cells are destroyed, the ability of pancreas to secrete insulin in response to blood glucose levels is impaired, resulting in the disruption of glucose homeostasis. T2D is also related with glucose regulation process. Macrophage secretes TNF α that reduces the expression of glucose transporter (GLUT4) [1, 10]. In case of obesity, pro inflammatory M1 macrophages engaged in insulin resistance and T2D occurs [11]. Due to obesity, local inflammation and chemokine production is increased and circulating M1 macrophages is recruited. The cytokines from M1 macrophage causes impair glucose tolerance [12-14].

MACROPHAGE IN WOUND HEALING OF DIABETIC PATIENTS

Non-diabetic wound is cured rapidly than diabetic wound by the re-epithelisation, epidermal thickening and substantial granulation [13, 14]. CCL2 (Chemokine ligand 2) is a potent pro-inflammatory cytokine. Previous researches showed that CCL2 enhanced wound healing. In diabetic patient the expression of CCL2 is decreased that hampers the response of macrophages [13, 15].

PERITONEAL MACROPHAGE AND DIABETES MELLITUS

Streptozotocin (STZ) induced diabetic macrophage showed decreased phagocytic activity [16]. AEG (Advanced Glycation End Product) is formed by the combination of protein and fat with sugar in blood. Streptozotocin induced diabetic mice showed high level of AEG which can alter the rate of phagocytosis [16]. High level of blood glucose induces mRNA expression of cytokine gene in peritoneal macrophage of diabetic mice. It is also increasing the IL12 expression from peritoneal macrophage [17].

Diabetes promoting chemicals (Streptozotocin, Alloxan) showed toxic effect in pancreatic β cell by producing superoxide anions, peroxy nitrite and nitric oxide that are free radicals (reactive oxygen species and reactive nitrogen species) [18, 19]. Our previous study clearly indicated that alloxan treated diabetes adversely affects peritoneal macrophages in rat. [20]. Significant numbers of peritoneal macrophages were found to be pyknotic. Alloxan treated macrophages showed membrane blebbing and nuclear degeneration. Diabetic rat peritoneal macrophages exhibited different phases of cellular death like formation of membrane blebs, rupture of plasma membrane and release of cytoplasmic contents [20]. It indicated the cells undergoing apoptosis or necrosis. Peritoneal macrophage death was also confirmed by trypan blue staining. It was calculated by mortality index which was significantly increased in diabetic group [20]. Our previous experimental study on rat showed alloxan treated liver was associated with partially low hepatic glycogen levels (as indicated by PAS response) [21]. This condition may be related with decrease of glucose tolerance [21]. In conclusion, our results showed that alloxan diabetes influence pancreatic islets morphology concomitant with cytomorphology of peritoneal macrophages. Considering that macrophage is an important component of the immune system, suppression of macrophage viability may illuminate the increased susceptibility of diabetic patients to infection [20].

We performed laboratory experiments using albino rat as a mammalian model. Rats were divided into experimental and their respective control groups. Group I animals were treated with streptozotocin (STZ) to make them diabetic. Activated charcoal particles suspended in normal saline (0.9% NaCl) was injected into rat peritoneum and the aspirate was taken for macrophage study. Significant changes were observed in the cytomorphology of peritoneal macrophages in the experimental group. Treated macrophages showed apoptosis, necrosis and paraptosis (cytoplasmic vacuolation) like features. Significant number of macrophages in diabetic group was not able to phagocytose the charcoal particles. Few diabetic peritoneal macrophages were completely laden by charcoal particles (pictures not shown).

DIABETES NEPHROPATHY (DN)

It causes the failure of kidney and more than 40% people are affected by DN in the United States [22, 23]. Macrophage influences podocyte to become more permeable & alternate its integrity. Kidney of diabetic patients shows thickened glomerular basement membrane, glomerular hyper filtration that leads to glomerular sclerosis. Glomerular macrophages are accumulated in DN [22, 24]. Glomerular macrophage secretes lysozyme, NO, ROS, $\text{TNF}\alpha$, IL1 [22, 25] that play important role in DN. Macrophage also reduces the expression of nephrin and podocin (which are very important protein for proper functioning of renal filtration barrier) in kidney of diabetic patients [22, 26, 27]. A therapeutic approach of DN can be achieved by inhibiting the chemokine released by macrophages [22].

DIABETIC RETINOPATHY

Diabetic retinopathy leads to the breakage of retinal barrier, it shows ocular inflammation and ultimately visual loss occurs [30]. Macrophage releases cytotoxic substances and ROS that ultimately leads to the neuronal damage [28]. Different stages of diabetes show activation of microglia in human retina and the accumulation of macrophage in the outer layer of retina and sub-retinal space [28, 29].

NEURO-INFLAMMATION AND T2D

Inflammatory macrophage in sciatic nerve promotes the neuropathic pain in T2DM. Accumulation of inflammatory macrophages was found in sciatic nerve. They express some chemokine that enhance neuro-inflammation associated with T2D [30].

M2 MACROPHAGE IS CRITICAL FOR BETA-CELL THERAPY

Exogenous insulin administration does not sufficiently replace the functional deficit of pancreatic beta cells in diabetes. The cure for diabetes would ideally require either replacement or regeneration of insulin-producing beta cells [31, 32]. In rodents, researchers suggest that beta-cell replication, rather than differentiation from progenitor cells, is the main contributor to beta-cell mass increase [33, 34]. Previous studies suggested that partial pancreatic duct ligation (PDL) which causes pancreatic tissue damage [31, 35] is accompanied by infiltration of inflammatory cells and M1 macrophages. There are also M2 macrophages which appear later to mediate tissue repair [36]. M2 macrophages are known to secrete a wide range of chemokines, and growth factors to promote neovascularization, fibrosis, and tissue repair [36]. It has been found that blocking pancreatic macrophage infiltration after PDL completely inhibited PDL-triggered beta-cell proliferation. M2 macrophages induce SMAD7 expression in beta cells. SMAD7 not only activates cell cycle activators (CyclinD1 and CyclinD2) but also induces the nuclear exclusion of cell cycle inhibitors to promote beta-cell replication [31]. So, M2 macrophage can be used as target for beta-cell therapy in diabetes.

Clinical therapeutic efficacy was assessed by researchers after adoptive transfer of M2 macrophages (Macrophages stimulated with IL-4/IL-10/ TGF- β) in NOD (non-obese diabetic) T1D mice, and after a single transfer, 80% of treated NOD mice were protected against T1D [37, 38]. Adoptive cell transfer of macrophages with immunosuppressive properties represents a novel immunotherapy for treatment of such chronic autoimmune diseases [37, 38].

CONCLUSION

Macrophage plays important role in T1D & T2D. Chemokine and cytokine from macrophage also affect the glucose uptake receptor. On the other hand, diabetes mellitus (DM) also alters the phagocytic capability and recruitment of macrophage in islets of Langerhans. Macrophage may help to provide novel therapeutic avenues for treatment of DM. However, further study and research are required to solve the paradox.

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