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COMMENTARY

Macrophages in diabetes mellitus (DM) and COVID-19: do they trigger DM?

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Abstract
Diabetes mellitus (DM) augments the risk of hospitalization and mortality resulting from viral, bacterial, or fungal pathogen infection. This has been also true for the past SARS and MERS, and current SARS-CoV-2 coronavirus epidemics. Clinical data indicate that SARS-CoV-2 infection triggers a severe course of COVID-19 more frequently in diabetic than non-diabetic patients. Here we overview the cellular and molecular mechanisms associated with this phenomenon. We focus on alterations in the immune cells, especially monocytes and macrophages, involved in innate immune response and inflammatory processes, which differ in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). We also describe the DM-related changes in the monocyte/macrophages functions, how they could lead to the severe outcome of SARS-CoV-2 infection, and importantly, if and how they could initiate DM in DM-susceptible patients.

Keywords Diabetes mellitus · Macrophages · SARS-CoV-2 · COVID-19

Pancreatic macrophages

Diabetes occurs when the excess of glucose accumulates in the blood because the pancreas, an organ responsible for the homeostasis of glucose in the bloodstream, is not producing enough insulin. The pancreas is a heterocrine gland that has food digestive (exocrine) and hormonal (endocrine) function. In its exocrine capacity, the pancreas produces hormones insulin, which lowers glucose level, and glucagon, which raises glucose level, and somatostatin, which inhibits the secretion of insulin and glucagon. There are five types of cells in the pancreatic islets: β-cells secreting insulin; alpha cells secreting glucagon, delta cells secreting somatostatin, epsilon cells secreting ghrelin (a so-called "hunger hormone" that stimulates food intake, fat deposition and growth hormone release), and pancreatic polypeptide (PP) secreting cells, which regulate endocrine and exocrine secretory functions of the pancreas. In addition, the pancreatic islets contain a population of resident islet macrophages. The islet macrophages are self-renewed and are rarely, if not at all, replenished by the bone marrow/blood-derived monocytes (Carrero et al. 2017). Islet macrophages are situated in the vicinity of the blood vessels, and they communicate with the cellular and acellular components of the blood through the filopodia that extend to the lumen of the vessels. They also interact with the β-cells, capturing insulin and presenting it to the autoreactive $CD^{+}4$ T cells, which are critical for the immune response. Islet macrophages express both stimulatory and suppressive ligands and receptors, chemokines, and cytokines including IL-1β, TNFα, and a high level of major histocompatibility complex MHC-II, and as such are the key regulator of the activation and recruitment of the lymphocytes, and additional monocyte/macrophages into the islets during the infection (Calderon et al. 2011, 2015; Carrero et al. 2017; Ferris et al. 2017; Vomund et al. 2015). For example, Carrero et al. (2017) showed that in the autoimmune

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diabetes nude mouse model, the deepletion of the islet macrophages using monoclonal antibody against the macrophage colony-stimulating factor1 (CSF-1) receptor decreses a recruitment of T cells into the islets.

Pancreatic macrophages in Diabetes mellitus (DM)

Diabetes mellitus (DM) results from the loss of functional β-cell mass in the pancreas. There are two main forms of DM: type 1 diabetes mellitus (T1DM) or Insulin-Dependent Diabetes Mellitus (IDDM; which accounts for 5–10% of all diabetic patients) and type 2 diabetes mellitus (T2DM) also known as Noninsulin-Dependent Diabetes Mellitus (NIDDM; which accounts for 90–95% of all diabetic patients). Preclinical and clinical studies indicate that the increased numbers of innate immune cells, and produced by them inflammatory factors have causative and detrimental effects on the islets and β-cells in diabetes (Böni-Schnetzler and Meier 2019). Molecular mechanisms leading to β-cell failures and cell death by apoptosis in T1DM and T2DM are distinct. While T1DM is immune-mediated, T2DM is metabolic-, mostly lipid-, mediated, and associated with obesity. These two mechanisms differently affect not only β-cells, but also the accompanying immune cells including macrophages, which are involved in the inflammatory processes associated with DM (Eizirik et al. 2020; Ying et al. 2020). The β-cell apoptosis is driven by the increase in mitogen-activated protein kinases triggering ER stress and followed by the release of apoptotic signals from the mitochondria both in T1DM and T2DM. However, two different gene cascades seem to be involved in each case: inositol-requiring enzyme 1 (IRE1)-driven genes in T1DM and the protein kinase RNA-like endoplasmic reticulum kinase PERK/ Eukaryotic Initiation Factor 2 alpha (eIF2α)-dependent pathway in T2DM (Cnop et al. 2005; Eizirik et al. 2020). Both T1DM and T2DM also affect the function of resident and recruited monocytes/macrophages that are essential for the innate immune response, cytokine secretion, phagocytosis, tissue homeostasis, and remodeling (Murray and Wynn 2011). DM, mostly via high glucose levels, modifies monocyte/macrophage metabolism causing failures in the innate immune and inflammatory processes (Ayala et al. 2019; Casqueiro et al. 2012; Esper et al. 2008). This is due in part to the changes in macrophage epigenetic profile, which modify their predisposed inflammatory state (van Diepen et al. 2006). Some of the DM-induced changes in macrophage functions are common to T1DM and T2DM, and some are distinct. For instance, in both DM variants, the proinflammatory cytokine or macrophage migration inhibitory factor Mif, is highly expressed and its level is elevated in the serum. The studies in the mouse model showed that Mif plays a crucial role in macrophages and dendritic cells activation (another type of innate immune system cells), lowers the levels of inflammatory cytokines, hyperglycemia, specific pancreatic islet antigen- (PIAg-) IgG, and reduces macrophages infiltration into the pancreatic islets (Sánchez-Zamora et al. 2016).

T1DM causes specific signal transduction dysregulations in the macrophages. The comparison of bone marrow-derived macrophages (BMDM) and peritoneal macrophages in non-diabetic and diabetic C57BL/6 male mice, the animal model for T1DM, has shown, recently, the dysregulation of both Pl3K/AKT, ERK 1/2 and SAPK/JNK protein kinases pathways and the secretion of cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-10 (Galvão Tessaro et al. 2020). Thus, in the T1DM, the macrophage-dependent innate immune response is significantly altered. In T2DM, both macrophages and NK cells show important modifications in the abilities to chemotaxis, and phagocytosis (Lecube et al. 2011), the functions playing a pivotal role in the initial stages of the fight against infection. Decrease of these functions condemns T1DM and T2DM patients to delayed and weaker immune defense already in the initial stages of infection, including SARS-CoV-2, which is today of the particular interest.

However, macrophages can not only protect but also aggravate the DM by augmenting pancreatic islets inflammation, and affecting β cell proliferation (Ying et al. 2019). Studies in diabetes 1 mouse model showed that diabetes promotes an inflammatory monocyte/macrophage phenotype (Kanter et al. 2012).

These data indicate that although the macrophages can have both protective and destructive roles depending on the pathologic context (Ying et al. 2020), their function in DM is skewed toward the inflammatory (and eventually damaging) response.

Increased ACE2 expression in DM and the SARS-CoV-2 infection

Although the general understanding is that the frequency of microbial infections in diabetic patients is the same as in the general population, some studies are indicating that diabetic patients have a higher risk of infections (Casqueiro et al. 2012; Carey et al. 2018; Critchley et al. 2018). Most importantly everybody agrees that infected diabetic patients have higher morbidity and mortality. This is also true for coronaviruses infections, such as SARS, MERS, and the current SARS-CoV-2responsible for the current COVID-19 pandemic. The one of the resaons of high morbidity of COVID-19 is directly related to the overstimulation of lung macrophages and overproduction of inflammatory cytokines, a so called cytokine storm that results in the caute respiratory distress syndrome (ARDS) (Kloc et al. 2020). Higher probability for diabetic

patients to develop higher SARS-CoV-2 viral load and more severe symptoms are related to the increased expression of Angiotensin-converting-enzyme 2 or ACE2 – the receptor for coronaviruses entry to human cells (Roca-Ho et al. 2017; Yang et al. 2020; Fang 2020; Richardson et al. 2020; Erener 2020). ACE2 is expressed in the lung, heart, adipose tissue, kidney, pancreas (especially in β-cells), the luminal surface of the small intestine, and blood vessels (Hamming et al. 2004; Monteil et al. 2020; Ziegler et al. 2020). The ACE2 is also expressed in the macrophages and monocytes (Chen et al. 2020; Rutkowska-Zapała et al. 2015), and its expression is stimulated by the inflammatory signals, such as type I interferon, produced by macrophages (Ziegler et al. 2020) Moreover, the medications with which diabetic patients are treated, e.g. glucagon-like peptide I (GLP-1) agonists, or hypertension medications, and statins, increase the ACE2 expression even more (Drucker 2020). Thus, diabetic patients become not only the privileged target for SARS-CoV-2 infection, but they may also develop a higher viral load because of the overexpression of ACE2 viral receptors in many cell types, nurturing SARS-CoV-2 replication.

How can COVID-19 elicit DM?

The possibility that COVID-19 may elicit DM in susceptible patients has been evoked recently (Rubino et al. 2020; Caruso et al. 2020). It seems to be confirmed by recent case reports (Marchand et al. 2020). Such a hypothesis has been already proposed following the SARS epidemic in 2002 (Yang et al. 2010). As we wrote above, SARS-CoV-2 infects many types of cells expressing ACE2 receptors, including the macrophages and β-cell in the pancreas. We postulate that there are several plausible mechanisms responsible for the triggering of DM in COVID-19. One possibility is that, similar to the effect of SARS-CoV-2 in the lungs, the infection of pancreatic macrophages causes inflammatory cytokine and chemokines storm in the pancreas. This, in turn, recruits additional immune cells, including proinflammatory monocyte/macrophage, causing additional damage to the pancreatic islets and β-cells. The second possibility is that because macrophages and monocytes are motile, after being infected with SARS-CoV-2, they disseminate virus to the and within the pancreas (Klepper and Branch 2015). Another possibility is that the SARS-CoV-2 infection of the β-cells, directly damages them, causing apoptosis, and reducing β-cell mass in the pancreas. Although, this scenario seemed the least likely because the direct damage to the pancreatic islets should result in higher than the reported incidence of COVID-19-induced diabetes, however, recent data presented in Nature News indicate that indead, the SARS-CoV-2 may cause direct damage to the insulin producing β-cells (Mallapaty 2020). Although, most probably, the combination of these different mechanisms is responsible for the development of DM in COVID-19 patients further preclinical and clinical studies, and analyses are necessary to give definite answers.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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