

Time to Clear the Air! Unmasking the “Fourth” Face of Diabetes

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LETTER TO EDITOR

The incidence of diabetes mellitus (DM) is projected to hit 642 million in 2040, a 55% increase compared to the estimated incidence in 2015. In 2017 alone, global mortality of DM was estimated at 5 million [1]. By 2040, the incidence of multiple sclerosis (MS) will increase by 100% compared to the incidence in 2008 [2]. The burden of MS on caregivers, economy, and public health cannot be overemphasized. The increasing incidence and economic burden and the search for more effective treatment options provide substantial argument for the need to step up investigations on the molecular signatures responsible for the etiopathogenesis of these diseases. Though the molecular and signaling mechanisms are yet to be fully delineated, preliminary evidences strongly indicate that MS may be a form of DM.

The changes in insulin production and impaired sensitivity are respectively, caused by impairment in insulin producing β pancreatic cells and insufficient response of tissue receptors to insulin. DM causes multiple disorders in the body including the central nervous system (CNS). It was widely believed that CNS symptoms resulting from uncontrolled DM are due to the hyperglycemic effects on the brain [3]. This view, however, did not change even following the discovery of insulin producing neurons over 30 years ago [4]. Insulin generating neurons was not given much attention to the possible pathological role of cerebral insulin until the early 20th century when scientists began to identify critical role of the insulin producing neurons in maintenance of cognition in health and disease [5]. Indeed, ongoing discussion suggests that DM is a disease of the brain [6]. A growing body of literature data indicate that Alzheimer’s disease (AD) is type 3 diabetes due to the ability of DM to trigger AD development, in addition to the multiple molecular pathways shared by the two diseases [6]. Importantly, the identification of insulin producing neurons in multiple brain regions including areas implicated in AD diseases suggest a critical role of these neurons in the

etiopathogenesis of neurodegenerative diseases such as AD and MS.

MS is a demyelinating chronic inflammatory disorder of the CNS involving activation of immunocytes in response to the activity of autoantibodies (IgM and IgG) and autoantigens (myelin oligodendrocyte glycoprotein). Though the etiopathogenesis is as yet to be fully understood, available data indicate that MS involves activation of complement proteins such as C1q and C3, CD3+ T cells, helper CD4+ and cytotoxic CD8+ T cells, macrophages and microglia in the CNS. The result is elevation of the levels of cytokines including IL-17. Interestingly, increased levels of serum IL-17 have been reported in DM patients [7].

Data from population based and genetic investigations suggest that MS may be a type of DM [8]. Both DM and MS seem to have common neuro-autoimmune etiopathogenesis [9]. Truly, common genes responsible for the development of both DM type and MS have been identified [10]. Based on available data, we suggest that MS may be “type 4 diabetes”. This, undoubtedly, opens a new window of research that may unravel key molecular culprits and therapeutic target of MS.

The signaling pathways involving glycogen synthase kinase 3 (GSK-3), nucleotide oligomerization domain-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, and nuclear factor κ B (NF- κ B) [9, 10] may provide useful footprints and molecular pathways shared by MS and DM. Though several pathways have been suggested to mediate DM-associated neuroinflammation and MS molecular pathogenesis [9], GSK-3 appears to be an integral culprit that triggers neuroinflammation observed in both diseases [10]. Accumulating evidences strongly indicate that activation of certain genetic variants of GSK-3, which is also involved in regulation of insulin signaling [10], can mediate the onset of MS. Being the most characterized inflammasome, NLRP3 promote infections and autoimmune disorders by enhancing the maturation of the pro-inflammatory cytokines by responding to pathogenic stimuli. Surely, NLRP3 activation has been reported in MS patients and DM [11], suggesting that this inflammasome may represent a key therapeutic target for treatment of MS and DM-associated

neuroinflammation. The certain variants of the NLRP3 gene predisposes to MS [11], though it is not exactly clear how NLRP3 inflammasome mediates onset or course of MS or DM-associated neuroinflammation.

The NF- κ B is a master player in inflammatory diseases, including MS. NF- κ B activation in oligodendrocytes has been reported in MS [12]. Furthermore, elevated NF- κ B activity has also been observed in T cells, macrophages, microglia, astrocytes, and neurons in MS and brain of DM patients or animal models [9, 12, 13]. Current MS therapy interferes with the NF- κ B pathways to modulate the patients' immune system [9]. Importantly, NF- κ B pathways is said to be modulated by a couple of microRNAs (neuro-immunoMiRs) including miR-146a and miR-155, which are also involved in both DM-neuroinflammation and MS autoinflammation and neurodegeneration [13].

In conclusion, both DM and MS are inflammatory diseases of the brain that involves direct or indirect impairment in cerebral immune and insulin signaling pathways. MS may represent a form of DM. Futuristic investigations on the molecular and signaling mechanisms of MS may provide plausible evidences to support this claim.

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