Editor’s Perspective

Heightened Attention for Wnt Signaling in Diabetes Mellitus

Life expectancy continues to increase throughout the world and is approaching eighty years of age for individuals [1]. Even in the United States (US), life expectancy is rising again, with a recent reduction in deaths from opioid overdoses [2]. If one considers developing countries, it is estimated that the number of elderly individuals, such as in China and India, will increase from five to ten percent over the next several decades [3]. Interestingly, in the presence of an increased lifespan, the ten leading causes of death remain unchanged. Cardiac disease, cancer, trauma, respiratory disease, stroke, Alzheimer’s disease, diabetes mellitus (DM), influenza and pneumonia, kidney disease, and suicide [1, 4-8] continue to remain the same [2]. Although many factors may account for the increase in lifespan in the presence of these disorders, it is believed that the expansion of preventive care to avert disease entities has contributed to the global increase in life expectancy.

The rise in lifespan throughout the world also has paralleled the increase observed with non-communicable diseases (NCDs). It is estimated that over forty million people die each year from NCDs [9]. NCDs affect a significant proportion of the population in low and middle-income countries with at least one-third of the population under the age of sixty suffering from NCDs. DM is a significant component of NCDs with almost 400 million individuals who are believed to suffer from metabolic disease and many are at risk for developing DM but presently are undiagnosed [1, 10-14]. In the US alone, at least seven million individuals over the age of 18 remain undiagnosed with DM and almost thirty-five percent of adults in the US have prediabetes [15].

Current treatments for DM are multifaceted and incorporate pharmacological treatments, nutritional programs, and activity regimens. Although these strategies can be effective for tight serum glucose control, the end-organ disease can continue to progress and affect all systems of the body. DM ultimately can lead to significant complications that include neurodegenerative disorders [16, 17], dementia [13, 18-20], cardiac disease [21, 22], renal disease [21, 22], and retinal disease [23-26].

Given these challenges, innovative strategies for DM are required to address disease progression and the complications of DM [27]. One such therapeutic avenue involves the pathways of Wnt proteins, proteins that are derived from the Drosophila Wingless (Wg) and the mouse Int-1 genes. Wnt proteins are cysteine-rich glycosylated proteins that play an important role in DM [27-31], vascular cell development [32, 33], immune function [34-36], tumorigenesis [37, 38], and neurodegenerative disease [24, 39, 40]. In addition to Wnt, other closely related pathways can serve to modulate cellular metabolism. For example, Wnt1 inducible signaling pathway protein 1 (WISP1), also known as CCN4, is a target of Wnt1 signaling that regulates programmed cell death, extracellular matrix production, tumorigenesis, and fibrosis [24, 41-45], but also is critical for metabolic function and DM [46-49]. As a result, Wnt, as well as the target pathways of WISP1, offer exciting prospects to develop new treatments for DM.

In this issue of Current Neurovascular Research, a number of exciting considerations to treat metabolic disease and the complications associated with such disorders are presented. New work suggests that the transient receptor potential melastatin 2 may play a role in DM and memory loss. Additional new studies also point to the sodium channel Nav1.7 that may be involved in peripheral neuropathies, applicable to complications of DM, though extracellular signal-related kinases. Yet some studies involving sodium channels, and investigations with riluzole, a drug that blocks tetrodotoxin-sensitive sodium channels and may inhibit the kainate and N-methyl-D-aspartic acid (NMDA) receptors, illustrate a lack of efficacy for this particular agent to prevent central and peripheral neuronal injury in experimental models of amyotrophic lateral sclerosis. These studies suggest that specific pathways tied to sodium channels may be at play to affect metabolic disorders linked to neuronal cell loss. Research works on this issue also extend to other factors associated with metabolic disease, such as the immune system. New works demonstrate that immune modulation can prevent blood barrier disruption during cerebral ischemia. In addition, pathways such as protein kinase B (Akt) [13, 50] that has a critical role in DM appears to be involved in the maintenance of cognitive function during cardiopulmonary bypass. This issue of Current Neurovascular Research has stimulating articles covering the neuremodulation of memory formation as well as examining both the potential and challenges for WISP1 derived therapeutic strategies for DM. Yet, future work is necessary to gain a better understanding of the neuropharmacological mechanisms that control memory encoding and retrieval. In a similar manner, WISP1 offers great promise for the development of effective treatments for DM, but clinical applications must be carefully crafted to avoid potential adverse effects given the close association of WISP1 with other critical determinants of cellular metabolism that include Akt, mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), silent mating type information regulation 2 homolog 1 (Saccharomyces cerevisiae) (SIRT1), and mammalian forkhead transcription factors (FoxOs).


