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Molecular mechanisms of diabetic neuropathy: From clinical practice to bench studies

Diabetic neuropathy (DN) is one of the most prevalent complications from type 2 diabetes. Up to 26% of patients with diabetic neuropathy from type-2 diabetes report a significantly decreased quality of life caused by painful diabetic neuropathy (PDN). The development of mechanism-specific treatments for PDN is in an urgent need. To determine the molecular mechanisms that mediates the development of PDN in patients with type-2 diabetes. We collected skin biopsies from patients with PDN and performed novel biomarkers studies to examine intra-epidermal nerve fibers (IENF). Our results demonstrated increased biomarkers of neural regeneration (GAP43) and degeneration (axonal swelling) in patients with PDN compared to DN patients have no neuropathic pain. To further establish the molecular signaling pathways that contribute to PDN, we used db/db mouse as a mouse model. We examined the gene and protein expression of dorsal root ganglion neurons and concluded that nerve growth factor/Trk A/p38 signaling pathway is essential for the development of PDN in db/db mice. This activation of this pathway leads to increased nociceptive nerve regeneration and proinflammatory cytokine-mediated inflammation in IENF. We also detected reduced expression of interleukin (IL)-10, an anti-inflammatory cytokine during the period of PDN in db/db mice. Exogenous IL-10 treatment significantly inhibited up-regulation of NGF, TNF-α and reduced PDN in db/db mice. In addition, the activation of Langerhans cells, the dendritic cells in the skin, during the period of PDN was reduced by IL-10 treatment in the hind paws of db/db mice. Our studies demonstrated the dysregulation of NGF-dependent cytokine-mediated inflammation contributes to the development PDN in type-2 diabetes. Our results will lead to new therapies that target this pathway for treating PDN of type-2 diabetes.

Biography

Hsinlin Thomas Cheng is the Director of Headache and Neuropathic Pain Unit, Massachusetts General Hospital and an Assistant Professor of Harvard Medical School. He is board certified in Neurology and Pain Management. His research interests include studying the molecular mechanisms of headache and neuropathic pain to establish new therapeutic treatments.

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