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Short Commentary

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TJP1 is a New Gene Target in Personalized Medicine

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Commentary

Dear editor, our research group studied the gene TJP1, (gene of narrow binding protein type 1, TJ) which encodes a protein of the tight junctions that form the zonula occludens. It is known that the TJP1 gene codes for a protein of the tight junctions that make up the ZO-1. The architecture of the tissues as well as the transcelular and paracellular transport in many tissues is closely related to the adequate function in the tissues [1]. One of the most important sites where this architecture needs to be maintained is the blood brain barrier which regulates the transport of drugs, microbial and nutrients to the central nervous system. In the BBB, TJs, particularly TJP1, plays a crucial role; its architecture is disrupted in several neurodegenerative diseases [2], such as cerebral ischemia, stroke, vasogenic edema, brain trauma, epilepsy, Alzheimer, Parkinson's disease, amyotrophic lateral sclerosis among others. The changes of the BBB takes place due to a lost of the permeability of the barrier and phenotypical changes in both the endothelial cells and astrocytes [3-5]. Also, it was hypothesized the susceptibility of barrier structure to metal toxicants permeability of brain barriers to any chemical is directly associated to the integrity of the endo/epithelial tight junctions and the proteins that construct them, claudins, occludin, junctional adhesion molecule, and membrane associate guanylate kinase proteins such as ZO-1 [6]. The response to treatment in dementia syndromes associated with nutrient deficiency or metal poisoning could be directly related to variations in the genes of the TJs such as TJP1 as well as those related genes that interact with them and with those molecules that transport neurotransmitters (Slc6a6, Slc6a17), thiamine (SLC19A3), nucleotides (SLC25A33), carnitine (SLC25A20), zinc (SLC20A1, SLC39A10) and riboflavin (SLC52A2/GPR172B), LRP1, LPRP8 and other as reported by Huntley in 2014.

On the other hand, drugs cross epithelial and endothelial sheets for two routes available: transcellular and the paracellular pathways. These transport mechanisms are mediated by hydrophilic molecules because they cannot cross biological membranes; therefore, their transepithelial transport could be significantly enhanced if they moved through the paracellular pathway [7]; the transit through this route is regulated by Tight Junctions (TJs). With the above considerations, TJP1 could be a new gene in pharmacogenetic studies in patients who have previously been diagnosed neurodegenerative diseases. Genetic variants could be a factor that influences the response to pharmacological treatment or the progression of these diseases. In this sense there is a study with SNP rs711355, rs785423, rs813676 which are associated with global impression severity during risperidone treatment in psychiatric patients [8].

It would be worth analyzing the pathogenic SNPs related to albuminuria in the Mexican-American population [9]. These also may have an influence on the response to pharmacological or clinical treatment in neurodegenerative disease, such is the case of the polymorphism rs229166 that leads to a conformational change in the ZO-1 structure [1], since this change could be related to the decrease or flow of transcellular or paracellular drugs. Some of those polymorphisms that lead to amino acid changes in critical domains or conserved domains of the protein ZO-1, are rs1038306187 leading to the change of amino acid p.Gln791Glu in the domain guanylate kinase (residue 682-861). Also, the domain ZU5 (residue 1701-1799) has 33 polymorphisms leading to conformational changes; all these markers must be taking into

account for the pharmacogenetic assay [4].

Statins (including atorvastatin) have several uses, the control of hypercholesterolemia, for the reduction of cardiovascular risk and the stabilization of the plaque of atherosclerosis in patients with acute coronary syndromes such as unstable angina, these three factors are related to the risk of cerebral vascular disease, cerebral infarcts, and cerebral vasogenic edema. The use of statins reduces the risk of these cardiovascular alterations. Recently it was reported that TJPs (Zo-1, Claudin-1 and Occludin-1) protein and Gap junction (GJP) (Cx43 Cx45 and Cx46) family play important roles in heart and blood vessel function and health. The Changing in TJPs and GAPs may have effects on Ankylosing spondylitis pathogenesis. In rat model on a high-fat diet, the formation of atheromas increased significantly; the artery wall was infiltrated with adipose tissue in histological section, heart coronary and artery endothelial tissue showed that Cx43/45/46 and claudin-1 were significantly down-regulated in coronary artery, the primary endothelial cell showed higher permeability,less Cx43 and Zo-1 protein expression and more CD14 monocyte penetration in heart and aorta was demonstrated by immunofluorescence staining,for those findings it was suggested that atheroma formation might be due to the loss of TJP and GJP, causing higher permeability in rat coronary artery and thus promoted the pathogenesis of atherosclerosis [11]. In effect, the polymorphisms of TJP1 that lead to conformational change could affect the permeability or function of the TJs influencing both the response to treatment to statins, the inflammatory myositis as well as being predictors in the prognosis and estimation of cardiovascular risk in patients with cerebral vascular disease or vascular dementia.

The discovery of the molecular mechanisms of the TJs, such as TJP1, has allowed the design of different procedures to open the paracellular route in a reversible manner. These strategies at the molecular pharmacology level could be used to enhance drug delivery across epithelial and endothelial barriers. The procedures suggested by our group include the use of peptides homologous to external loops of integral proteins, the use of antisense oligonucleotides and siRNAs to silence the expression of TJ proteins as well as the use of toxins and proteins derived from microorganisms that target TJ proteins [7]. In this sense we analyze the interaction of the SNP commented on TJP1 with the SNP rs767649 of miR-155 which regulates the expression of TJP1 [13].

The gold standard in the pharmacogenetics of cancer is the MDR1 gene, which codifies a membranal drug transporter. TJP1 could be useful in studying the response to cancer treatment and prognosis since in different types of cancer its expression is altered, or its protein encoding is disrupted [1,10].

With all the previously above mentioned, it is important to consider TJP1 in the postgenomic era since it is a housekeeping gene, and they have multiple pleitropic effects, which is why it is an ideal pharmacological target, but it will have to remain explored

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