G protein signaling: a major culprit of essential hypertension

Blood pressure (BP) is the driving force that distributes the blood to the organs of the body according to their instantanous needs. It may be increased by pressor agents acting on the heart, vessels, and blood volume, in response to physical needs and psychological stress. Most of these pressor agents bind to receptors located on the cell surface and their signals are transmitted into the cell through G proteins, molecular switches that transmit the signals from a variety of stimuli outside the cell to its interior.

Abnormalities of G protein coupled receptor signaling may cause essential hypertension, a chronic elevation of BP associated with increased risk of cardiovascular complications (stroke, heart failure, myocardial ischemia, and kidney damage) that results from the interaction of genetic and environmental factors.

The GNB3 gene, coding for the ?3-subunit of G proteins, is highly polymorphic, with one polymorphism (C825T) associated with alternative splicing of the gene. Alternative splicing gives rise to a G?3 protein which lacks 41 aminoacids and it is, therefore, short (G?3s). Expression of G?3s results in a dominant gain of function, that is, it increases signal transduction within the cell.

Increased G protein activation, caused by the expression of the more active G?3s in the carriers of the 825T allele, is associated with reduced blood perfusion of the heart and of the skin, increased prevalence of hypertension, obesity, and insulin resistance, the typical hormonal profile of type 2 diabetics. The whole of these results suggested to us that the C825T polymorphism indicates high risk of cardiovascular complications.

Ten years after our hypothesis we reviewed the literature to verify whether this was the case. To do so, we collected all the studies that reported cardiovascular morbidity and mortality in relation to GNB3 C825T polymorphism. These studies include both genders from different geographical areas, and have a case-control or longitudinal design. In longitudinal studies enrolling 9579 Caucasian or Japanese patients for a median follow up of 7 years, we found that the carriers of the T allele have increased morbidity and mortality for myocardial infarction and stroke.

This is not the only evidence for a critical role of abnormal G protein signaling in causing hypertension and its cardiovascular complications. G protein signaling is switched off by small proteins called RGS (regulators of G protein signaling). RGS2 is a negative regulator of G?q protein signaling, which mediates the action of several pressor agents, and low RGS2 expression increases G-protein-coupled signaling in hypertensive patients. RGS2 expression, also, affects the response to antihypertensive treatment and reduced RGS2 expression contributes to resistance to antihypertensive agents because stimuli that increase BP cannot be blocked. More data will come out. Stay tuned.

Andrea Semplicini *MD*

Department of Medicine, University of Padua, Italy

Publication

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