Commentary

Many Channels Lead to Aldosterone☆

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Aldosterone secretion is under the control of potassium, renin and angiotensin (Ang II). Consequently, concepts to explain autonomous aldosterone secretion as the basis for primary aldosteronism (PA) included the presence of stimulating autoantibodies to the Ang II type 1 receptor (AT1R), gain-of-function mutations in the AT1R and aberrant expression of G-protein-coupled membrane receptors that are responsive to alternative stimuli and have access to the cellular AT1R signaling apparatus (Luft, 2013, Mazzuco et al., 2010). However, while these ideas are great the power to explaining the pathophysiology of PA remained small. The breakthrough came with the systematic clarification of signaling pathways which control aldosterone secretion, the application of whole exome sequencing to adrenal disease and the discovery that signaling pathway variations and detectable by means of in vitro investigations into channel properties, calcium signaling, steroidogenic enzyme expression and aldosterone secretion into cell culture supernatants. While the patients with a mild mutation did not, the subject with the severe CACNA1H mutation had early onset PA and multiplex developmental disorder. Interestingly, pathological neurologic features had been reported to occur in patients with PA due to a CACNA1D mutation which is also known to strongly affect intracellular calcium within zona glomerulosa cells (Scholl et al., 2013). The tumors of such patients are comparably small but show strong expression of aldosterone synthase and suppression of renin. Interestingly, it was suggested that some mutations may severely interfere with the cellular calcium homeostasis and even cause the death of an affected adrenocortical cell thus preventing the cell from developing hyperplastic or tumorous tissue.

However, less severe aberrations, including some mutations in the G protein–activated inward rectifier potassium channel 4 (GIRK4) potassium channel, seem to be associated with a milder phenotype of PA, larger tumors and expression of aldosterone synthase in the remaining normal zona glomerulosa tissue as a sign of non–(full) suppression of renin and angiotensin. This may explain why in tumors of patients with malfunctioning GIRK4 channels, the 11beta-hydroxylase is expressed at higher levels within the aldosterone-producing tumors and that such patients form more so-called “adrenal hybrid steroids” than patients with aldosteronomas due to CACNA1D mutations (Fig. 1) (Williams et al., 2016).

Along these lines, it seems to be very difficult to characterize the point of crossover from a single-nucleotide polymorphism to a mild disease-triggering mutation by means of such studies. An astonishing observation in this context is that mutations which are associated with the formation of aldosterone-producing adenomas were also observed in bilaterally hyperplastic adrenals and may even appear within different nodules in one adrenal gland although each nodule seems to harbour only one single mutation (Fernandes-Rosa et al., 2015). As such it remains open how channelopathies associated with PA – whether inborn or acquired – allow the affected adrenal cell to proliferate and break away from aldosterone-producing cell clusters in order to form aldosterone-producing adenomas.

So far, conventional cell culture studies did not provide the data to reach conclusions on how such mutations cause growth and
proliferation of adrenal cortical cells. This may be because the influence of corticotropin, adrenal blood flow and tissue gradients also seem to play an important role in organ physiology and cell differentiation (Dringenberg et al., 2013). Therefore, while this study bridged the gap between clinical observations, the molecular background, its impact on cell physiology and aldosterone secretion, further such studies should address the question how the molecular changes promote cell proliferation and adrenal tumor formation.

Disclosures

The author declares no competing interest.

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