Universität Basel

Research Project

The role of mTOR in pathophysiology of primary aldosteronism

Third-party funded project

Project title The role of mTOR in pathophysiology of primary aldosteronism
Principal Investigator(s) Hall, Michael N. ;
Co-Investigator(s) Swierczynska, Marta ;
Organisation / Research unit
Departement Biozentrum / Biochemistry (Hall)
Department
Project start 01.01.2017
Probable end 31.12.2017
Status Completed

Primary aldosteronism (PA) is a disease characterized by inappropriately high aldosterone production by the adrenal gland. It is the leading cause of endocrine hypertension affecting up to 20% of the hypertensive population. In addition to increased blood pressure, PA is associated with an increased risk of cardiovascular and renal complications that can be prevented/reversed by appropriate treatment. Unfortunately, treatment options are limited and do not cover the needs of all patients.ă Additional treatment options are needed.

PA etiology is poorly understood. However, recent findings suggest the involvement of mammalian target of rapamycin (mTOR), a conserved kinase and a central controller of cell growth. It has been demonstrated that mTOR is hyperactive in the adrenal glands of PA patients and regulates proliferation, apoptosis and hormone production by adrenal cells. Our *in vivo* data show that systemic mTOR inhibition decreases circulating aldosterone but not other steroid hormone levels.ă However, the molecular events leading to PA-■related mTOR hyperactivation and mechanisms of mTOR action in adrenal cells have not been studied.

Our aim is to comprehensively analyze molecular events that lead to mTOR disturbances in PA. We propose to elucidate the mechanism of mTOR action in adrenal gland pathophysiology and to evaluate mTOR inhibition as a therapeutic strategy for PA.

To identify molecular disturbances underlying PA-■related mTOR deregulation, we will subject resected aldosterone-■secreting tumors and matched control adrenal tissue to proteome and phosphoproteome analyses.ă We will establish primary cell lines from aldosterone-■producing tumors and assess their proliferative and aldosterone-■producing potentials in response to mTOR inhibitors. Treated cells will be subjected to transcriptome, proteome and phosphoproteome analyses to identify the downstream targets of mTOR signaling in adrenal cortex cells. The functional contribution of specific signaling disturbances identified through these “omics” approaches will be evaluated in well-■established adrenal cell lines.

The proposed study will

a) identify and characterize signaling defects underlying PA-■related mTOR disturbances,

b) reveal the role of mTOR in adrenal pathophysiology,

c) evaluate a novel treatment for PA based on mTOR inhibition, and

d) potentially identify novel targets for PA treatment.

Keywords mTOR, adrenal gland, primary aldosteronism
Financed by
Foundations and Associations

Add publication

Add documents

Specify cooperation partners