Protein Kinase A (PKA) in Health and Disease: An integrated approach from disease predisposition to the design of new treatments around a key enzyme

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ABSTRACT

Protein kinase A (PKA) was identified in 1968 as the long-sought target of the second messenger molecule cyclic adenosine mono-phosphate (cAMP). PKA is a serine threonine kinase involved in the regulation of many cell signaling pathways and has a tetrameric structure composed of a regulatory dimer and two catalytic subunits. There are four regulatory and five catalytic subunits, each coded by their own genes. The first disease linked to PKA was Carney complex that causes multiple tumors. More human diseases and neoplasms have been linked to PKA subunits since. In addition, mouse models show involvement of PKA subunits in a number of traits, from voluntary exercise to predisposition to obesity and metabolic syndrome, susceptibility to certain viral infections etc. This work aims at supporting a PKA-centered investigation of molecular, human and animal phenotypes that could be linked directly or indirectly to PKA and its function, through the use of state-of-the-art technologies, including genomics, animal modelling and identification of small molecules that could be used as pharmaceutical targets and possibly advance to clinical trials. We have already identified compounds that may inhibit the main catalytic subunit of PKA, PRKACA. If successful, PRKACA inhibitors may be used from treating rare diseases like Cushing syndrome to various common neoplasms where PKA activity is found activated. Other PKA inhibitors may be used for the treatment of metabolic syndrome and/or obesity, as well as to prevent fatty liver and its complications. This work will (1) advance our basal knowledge of cAMP and PKA signaling (2) provide molecular markers for predisposition to diseases or specific phenotypes; and (3) lead to the development of a new class of therapeutic targets linked to one of the first serine-threonine kinases ever studied which, however, has been left behind over the years and not exploited as a target for its therapeutic potential. PKA is involved in several cellular functions, not only as the main mediator of cAMP signaling, but also interacting with other serine-threonine kinases and even involved in the regulation of tyrosine kinase signals, acting on the control of cell growth and proliferation, the cell cycle, hormonal secretion and action, and beyond. As such, our work aims at establishing a PKA-centric approach to study a variety of human phenotypes and develop methods to study it and potentially new therapeutic approaches. Indeed, the first diseases linked to PKA subunit defects are associated with human neoplasms and abnormalities of the endocrine system (Carney complex, pituitary and adrenal tumors, adrenocortical cancer), but PKA (and related) variants have now been associated with metabolic syndrome, non-alcoholic fatty liver disease, ageing, addiction, and even viral infections.

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