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Differential inhibition of PDKs by phenylbutyrate and identification of putative binding sites

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Pyruvate dehydrogenase kinase (PDK) isoforms are molecular switches that downregulate the pyruvate dehydrogenase complex (PDC) by reversible phosphorylation in mitochondria. To date, four PDK isoforms (PDK1-4) have been identified in humans, each of them is able to phosphorylate (and inactivate) the complex exhibiting different site specificity. The expression of the four PDK isoforms is tissue specific in response to needs of various tissues under different metabolic conditions. Indeed, their activity on PDC is an important switch that regulates both diabetes (PDK2/PDK4) and cancer metabolism (PDK1/PDK3). So far, several molecules have been investigated to inhibit PDK activity but none of them fulfils the requirements for a safe and effective drug: strength, specificity, and absence of toxic effects. The author and her team has recently discovered that phenylbutyrate (PB) is effective in activating the PDC by direct inhibition of PDK2 and is effective at improving a rare inborn error of metabolism due to PDC deficiency. In this it has been investigated phenylbutyrate inhibiting activity towards the other PDK isoenzymes (PDK1, 3 and 4) using suitable functional assays. Also, by using molecular docking, we have identified putative binding sites of PB on each PDK isoform suggesting molecular determinants of enzyme selectivity. The information gained from these studies give important insights on the molecular determinants in PDK inhibition and allows designing specific PDKs inhibitor. Also, because PB is already approved for human use in other diseases, the findings of this study have the potential to be rapidly translated into clinics.

Biography

Clara Iannuzzi obtained a degree in Chemistry at University Federico II of Naples (Italy) in 2002 and a PhD in Cellular Biochemistry at Seconda Università di Napoli (Italy) in 2006. Between 2006 and 2012 she held a Career Development fellowship at MRC-National Institute for Medical Research in London (UK). At present she is Researcher at Seconda Università di Napoli and Associate Researcher at CNR- Institute of Protein Biochemistry (Naples, Italy). She has published many research papers on peer-reviewed journals in the field of biochemistry and molecular biophysics.

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