Editorial

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Molecular Enzymology and Drug Targets

2017
Vol.3 No. 1:e105

DOI: 10.21767/2572-5475.1000e105

The Crucial Roles of Enzymes Belonging to Signal Transduction Pathways. Old Molecules as New Therapy Molecular Targets. Approaches, Perspectives and Criticisms

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Received date: May 4, 2017; **Accepted date:** May 6, 2017; **Published date:** May 8, 2017

Citation: Lo Vasco VR (2017) The Crucial Roles of Enzymes Belonging to Signal Transduction Pathways. Old Molecules as New Therapy Molecular Targets. Approaches, Perspectives and Criticisms. Mol Enz Drug Tar 3: e105

Editorial

The crucial roles of Enzymes belonging to signal transduction pathways. Old molecules as new therapy molecular targets. Approaches, perspectives and criticisms.

Since last ten years the observation that most of the human diseases can be considered "signaling diseases" was corroborated by many reports. In this perspective, increasing evidences demonstrated a crucial role for "signaling enzymes", the wide number of enzymes involved in specific steps of signal transduction pathways. Many different families of enzymes are involved in a variety of signal transduction pathways. In a signaling system, enzymes are main actors which play important roles, regulating the metabolism and concentration of further signaling molecules. Thus, different families of enzymes regulate a wide number of cell or tissue activities. As one example, enzymes belonging to the Phosphoinositide-specific Phospholipase C (PLC) family were reported to be involved in many key functions such as intra-cellular signaling, membrane trafficking, nuclear signaling based on lipid hydrolysis in response to a wide panel of stimuli, including growth factors, hormones, and neurotransmitters, that act on specific receptors localized at the plasma membrane.

More recently, specific signal transduction pathways were reported to be involved in human diseases. Following those numerous and randomly distributed repots, cell or animal models were developed evaluate the role, involved molecules and meaning of the disruption of specific signal transduction pathways. In this perspective, PLC enzymes were reported to be associated to the transition from myelodysplastic syndrome to acute myeloid leukemia, to different tumors, both in humans and in animal models, to nervous diseases, including tumors, schizoaffective disorders, mental retardation, as well as epileptic encephalopathy, to cardiac problems, and skin disorders.

PLC enzymes belong to the phosphoinositide (PI) signal transduction pathway. All PLC isoenzymes share the same main activity. Activation of a PLC enzyme leads to cleavage of the phosphatidyl inositol 4,5 bisphosphate (PIP2), a crucial molecule in the PI system, located in the inner half of the cell membrane. Cleaving of the polar head of PIP2 triggers the production of two further signaling molecules, Diacylglycerol (DAG) and Inositol trisphosphate (IP3). Although all PLC enzymes act cleaving PIP2, the activation differs. Therefore, each isoenzyme probably bears unique functions, related to the different mechanisms of activation. Thus, the mammalian PLC family of enzymes, comprising of 13 isoenzymes, was subdivided into 6 subfamilies, differing for specific domains' presence and activation stimuli. Each subfamily comprises of isoenzymes sharing similar aminoacids sequence, domain organization, and mechanisms of activation. The distribution of the PLC enzymes is strictly tissue specific. Each cytotype/histotype does not contain all 13 PLCs. On the contrary, each cell/tissue owns a specific panel of PLC enzymes. Moreover, the distribution of PLC enzymes was demonstrated to vary in pathological cells/tissues with respect to the normal counterpart. Different distribution of PLC enzymes was also reported in activated cells with respect to the quiescent counterpart, with special regard to inflammatory activated endothelial cells, astrocytes and macrophages.

Specific inhibitors are currently available for most enzyme families and, for a limited number, also activators can be used. Therefore, the possibility to block (or activate) selected enzymes offers the ability to control, regulate or modulate the activity of the whole signal transduction pathway the enzyme belongs to or, at least, to act upon a part of the system. For PLC enzymes, the use of specific activators or inhibitors of the enzymatic activity demonstrated a variation in the survival of cells or in the sub-cellular distribution of the enzymes. More recently, also epigenetic related methodologies (i.e. RNA silencing) allowed control signaling related enzymes. For PLC enzymes, blocking selected PLC isoenzymes, namely PLC, was demonstrated to modify the behavior of *in vitro* cultured human osteosarcoma cells.

Thus, to affect a signal transduction pathway blocking its enzymes can pave the way to molecular understanding of the pathogenesis of the disease. Moreover, it can open the way to novel therapeutic strategies, using the enzymes as molecular targets.

Limitations of this promising perspective can be represented by possible molecular switch of the pathway or trespassing the block, limited action due to the time-dependent activity of the inhibitors (or activators), and problems related to the *in vivo* translation of *in vitro* observations.

However, beside those criticisms, *in vitro* results are encouraging, also following the observation that inhibitors can also affect the gene expression of enzymes suggesting a longer-term activation.

Further studies are required in order to widen the knowledge of the disruption of signal transduction pathways in human diseases. New efforts are also required in order to evaluate the time related effects and kinetics of the modulators (inhibitors and activators) of signal transduction pathways with respect to related human diseases.

This article is available from: 10.21767/2572-5475.1000e105