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The Complementarity Effect for Cdc25 Phosphatase Inhibitors

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Abstract

Cdc25 phosphatase have been regarded as attractive drug targets for anticancer therapies due to the correlation of their over expression with a wide variety of cancers. They are key regulators of cell cycle progression and play a central role in the checkpoint response to DNA damage. The role of Cdc25 s in cancer has become increasingly evident in recent years. More than 20 studies of patient samples are from diverse cancers show significant overexpression of Cdc25 with frequent correlation to clinical outcome. Recent screening and design efforts have yielded novel classes of inhibitors that show specificity for the Cdc25 s over other phosphatases and cause cell cycle arrest *in vivo*. Until now, quinone derivatives are among the most efficient inhibitors of Cdc25 phosphatase activity. Our research objective is to study the inhibition of the phosphathase Cdc25 through the molecular modeling methods.

Keywords: Cancer, Cdc25 Phosphatase, Molecular Modeling (MM, DM, and Docking), Naphtoquinone

1. Introduction

Cancer is a group of diseases characterized by uncontrolled cell division leading to the growth of abnormal tissue. These cells known as "malignant" different from the normal cells, present anomalies of structure and behavior. They will upset the architectural order of the normal cells while piling up and by pushing back these last before invading them. The knowledge of the cellular cycle makes it possible to consider the various means to fight against this anarchistic proliferation [1]. Cancers and leukemia are diseases which can touch the child as well as the adult and which are characterized by an abnormal and anarchistic proliferation of "normal" cells in the organism:

- Cells of blood and osseous marrow for leukemia, cells of the lymphoid bodies (spleen, ganglia…) for the lymphomas.
- Specific cells or not of a body for the solid tumors (of the brain, the bone, of kidney…).

At the beginning of the 20th century, the objective of the researchers was to discover the agents that cause cancer. Thus much of heterogeneous factors can be at the origin of the development of tumors [2-5] which are the most known. Factors may be viral, chemical (benzene, aflatoxine), physical (ionizing radiations, ultraviolet light), traumatic, inflammatory, parasitic (tumors of the lip of the horse), skin cancer including burn scars [6] and nutritional ones [7,8].

Cdc25 phosphatases are dual specificity phosphatase. They play an essential role in cell cycle progression [9,10], There are three types of Cdc25 phosphatases in man: Cdc25A, B and C. [11,12] they have a structure and a common catalytic mechanism. These proteins are composed of 300 to 600 amino acids and can be divided into two parts:

- The C-terminus represents about one third of the enzyme and contains the catalytic site. The latter has a pattern common to all CX5R protéine tyrosines phosphatases where C is a cysteine catalytic X and R different amino acids arginine
- He N-terminus acts as a regulator. This is the part that differs most between different sub-classs of Cdc25. It contains many phosphorylation sites [13,14].

The catalytic mechanism of dephosphorylation by Cdc25 is similar to that of PTP1B [15]. After nucleophilic attack by cysteine followed by protonation, there is departure from the substrate and formation of an intermediate phosphate. Hydrolysis frees the phosphate phosphatase and return (**Figure 1**).

