TARGETING THE HSP90 INTERACTOME USING IN SILICO POLYPHARMACOLOGY APPROACHES

Hsp90 and its interactome represent an attractive array of targets for polypharmacological drug design strategies in cancer therapy. In this work, we propose a computational protocol aimed at the selection of promising target combinations and potential multi-target active compounds.

Introduction

In recent years, polypharmacology has gained popularity in drug discovery [1]. Especially for complex diseases such as cancer, the ability of a drug to bind to and interfere with multiple targets provides new opportunities for therapeutic intervention. In this article, we focus on Hsp90 and its interactome, whose pivotal role in survival and proliferation of cancer cells renders this array of targets particularly attractive for polypharmacological drug design strategies.

The primary goal of our work is the identification and selection of suitable target proteins from the interactome that might be combined with Hsp90 to explore and exploit a multi-target inhibition approach. This task is accomplished by applying computational methods to mine the structural and biological information associated with potential ligands in public databases and assess the degree of structural similarity between known inhibitors of different targets. Therefore, we propose an integrated ligand- and structure-based approach to select small molecules from databases suitable for consideration as multi-target inhibitors.

Biological background

Cancer is one of the world leading causes of death accounting for 7.6 million deaths in the year 2008. The number of deaths per year is projected to rise to 13.1 million in 2030 [2]. Both genetic and environmental factors may be at the origin of human cancers. In general, cancer cells are characterized by uncontrolled proliferation and survival. Indeed, several cellular pathways might be affected by this pathology contributing to the expression of the transformed phenotype. Heat shock response is often activated in cancer cells, contributing to both initiation and maintenance of the transformed phenotype. Hsp90 is an important component of this process, acting as a molecular chaperone affecting stability and activation of more than 200 client proteins through ATP hydrolysis cycles [3]. Proteins interacting with Hsp90 are often involved in signalling processes, such as transcription factors and kinases.

Polypharmacology and Hsp90

Popular computational methods applied in medicinal chemistry include ligand- and structure-based virtual screening. These techniques aim at finding new small organic molecules with specific activity against a given biological target. Typically, the target is a protein that might act as an enzyme, a receptor, or an ion-channel, whose activity is involved in a pathological mechanism. The interaction of the small molecule with the target is intended to interfere with the protein’s activity in a physiologically relevant manner. Following the classical drug design paradigm, the small molecule should be highly selective for the chosen target. Interactions with additional targets might be the cause of the so called off-target effects, which in turn might be responsible for toxicity and thus impair the development of a safe, marketable drug.

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Approcci polifarmacologici in silico mirati all’interattoma di Hsp90

Hsp90 ed il suo interattoma sono bersagli attrattivi per l’applicazione di strategie polifarmacologiche nella terapia antitumorale. In questo studio viene proposto un protocollo computazionale mirato alla selezione di combinazioni promettenti di bersagli e di potenziali composti attivi su bersagli multipli.

References