A Network-Based Approach To The Cancer Hallmarks Paradigm For The Localization Of Pharmacological Targets In The Human Interactome

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Background: In 2018 cancer was reported as one of the leading causes of death worldwide, responsible for the death of one in eight men and one in eleven women. In addition to this high prevalence and mortality, cancer appears as a complex phenomenon in its physiopathological mechanisms and highly heterogeneous and variable in its manifestations. These two factors lead to the need for new diagnostic and therapeutic approaches that allow us to study the complexity of this disease from a holistic perspective. In this research we provide an approach to this problem through the cancer hallmarks paradigm by the means of network analysis.

Methodology: For the purposes of this research, sets of genes associated with cancer hallmarks were established from scientific literature and database mining. These genes were used for the delimitation of modules in the human interactome. Metrics of overlap, similarity and distance of these modules were established in relation to a module constructed from the genes mutated in cancer, which fulfills the purpose of representing the etiology of the disease in the network. A list of pharmacological targets in cancer was constructed, from which it was evaluated whether the hallmarks were areas of high density of these in the network and, if so, whether this density was influenced by the relation of the hallmark modules and the module associated to the etiology of cancer. Finally, node-specific network metrics were evaluated as possible predictors of pharmacological targets within each module.

Results and conclusions: Our study shows that cancer hallmarks are areas of high density of pharmacological targets in the human interactome. This high density of targets in the hallmark modules is not related to their similarity, overlap or proximity to genes associated with the etiology of cancer. Finally, although all the specific network metrics for nodes evaluated as predictors showed predictive value, there was no substantial difference between them. Overall, the study reveals that the hallmarks can be good starting points for future pharmacological target prediction studies. It is suggested for future research to evaluate in greater depth the predictive potential of the node-specific network metrics evaluated during this study.

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