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Type	Oral communication
Session	Systems Biology
Title	Molecular mechanisms involved in oncological diseases investigated by a new multiple network-based bioinformatics pipeline
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Motivation

Assessment of genetic mutations is an essential element in the modern era of personalized cancer treatment. Our strategy is focused on "multiple network analysis" in which we try to improve cancer diagnostics by using biological networks. Genetic alterations in some important hubs or in driver genes such as BRAF and TP53 play a critical role in regulating many important molecular processes. Most of the studies are focused on the analysis of the effects of single mutations, while tumors often carry mutations of multiple driver genes. The aim of this work is to define an innovative bioinformatics pipeline focused on the design and analysis of networks (such as biomedical and molecular networks), in order to: 1) improve the disease diagnosis; 2) identify the patients that could better respond to a given drug treatment; and 3) predict what are the primary and secondary effects of gene mutations involved in human diseases.

Methods

The developed pipeline is characterized by a multi-step design, which concerns different biological-molecular networks (Fig. 1): disease-disease, gene-disease, gene-variant-disease, gene-gene, protein-protein interaction and multilayer drugs networks. The last three steps can be performed in both directions. All these steps have been performed through Cytoscape v3.7 Core (with its specific plugins used for the realization and analysis phase). The realization of the disease-disease network is focused on the comprehension of the disease at molecular level. This network allows to investigate the associations/correlations between the disease of interest and the other ones, trying to understand the disease progression and explaining the secondary symptoms that a patient could develop over time. Moreover, it allows to have a useful map that will help identifying the priority genes and hubs associated among the main disease and the others, creating the gene-disease networks and gene-variant-disease network. Both allow to generate the networks and extrapolate the information useful for pharmacological purposes to identify the best therapies for individual patients. Moreover, these networks are useful to identify which are the single/double/multiple clinically relevant mutations involved in the disease of interest, to select the most suitable therapy. After the study of the priority genes and of the mutations mainly involved in the disease, it is possible to create the gene-gene network, with the aim of understanding how the molecular profile of the network changes for the individual patient in the presence of one or more missense or other mutations. In this way, an analysis can be done on the joint effect derived from the combination of multiple mutations, creating the protein-protein interaction network using the gene-gene net as input. As a result, it is possible to trace the molecular mechanisms involved both at physiological and at pathological levels, evaluating the joint effects deriving from the presence of one or more mutations. Then, it is possible to identify which molecular mechanisms are changing and which could be the pharmacological therapies applicable for the individual patient. Once all the main networks are created, it is possible to create the multilayer drugs network. It contains all the information derived from the networks accomplished in the previous steps.

Results

By using the pipeline based on a multiple network approach, it has been possible to demonstrate and validate what are the joint effects and changes of the molecular profile that occur in patients with metastatic colorectal carcinoma (mCRC) carrying mutations in multiple genes. In this way, we can identify the most suitable drugs for the therapy for the individual patient. This information is useful to improve precision medicine in cancer patients. As an application of our pipeline, the clinically significant case studies of a

cohort of mCRC patients with the BRAF V600E-TP53 I195N missense combined mutation were considered.

Info

The procedures used in this paper are part of the Cytoscape Core, available at (www.cytoscape.org). Data used here on mCRC patients have been published in [Normanno N. et al. (2015)]. The data refer to a cohort of metastatic colorectal cancer patients (mCRC), treated with first-line FOLFIRI plus Cetuximab in the CAPRI-GOIM trial [Ciardiello F. et al (2014); Normanno N. et al. (2018)].
A supplementary file containing a more detailed discussion of this case study and other five cases will be available at the Briefings in Bioinformatics site as Supplementary Data of paper no. bbab180, in press.
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Figure

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Availability	-

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