Studying the Complete Interactome of Sirtuins

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Motivation

Sirtuins genes are widely distributed by evolution and have been found in eubacteria, archaea and eukaryotes. In humans as well as in all mammalia this family is composed by seven different homologous proteins being all NAD-dependent deacetylases/ADP-ribosyltransferases. Some studies have determined the cellular location of human SIRT families and their biological functions. SIRT1 is defined as a nuclear protein and is involved in inflammation metabolism and neurogeneration. SIRT2 is generally localized in the cytoplasm, and is involved in cell cycle and tumor genesis. SIRT3, SIRT4 and SIRT5 are mitochondrial proteins and, in particular, SIRT4 is a ADP-ribosyl-transferase enzyme, whereas SIRT3 and SIRT5 are deacetylases. Finally, SIRT6 and SIRT7 are nuclear proteins, associated with heterochromatic regions and nucleoli, respectively. SIRT6 controls DNA repair and has a ADP-ribosyl transferase activity, while SIRT7 is involved in rDNA transcription because acting on RNA polymerase I. The abundance of the cellular partners and the complexity of the metabolic network in which the sirtuins are involved represents the most important reason for which this protein family is very largely studied. Therefore aim of this work is to study the complete interactome of Sirtuins and to understand how their genes function and what genes interact with each other in major pathways.

Methods

Cytoscape software was used to analyze the network of Sirt family. In particular, the interactions of Sirtuin family were filtered from Bio grid, HPRD, MINT and Nature pathway Interaction Database. The interaction types taken into account were biochemical reactions, complexes, complex assembly, control reactions and physical interactions of the proteins. Protein-protein interaction network was obtained from University of Verona whereas gene-gene interaction network from Gene interaction Network of NCIBI (National Center for Integrative Biomedical Informatics). For Statistical analysis, Centiscape plugin (Giovanni Scardoni et Al.) is used which gives centrality statistics of the protein network. Particularly, the central vertices in complex networks were of particular interest because they might play the role of organizational hubs. Mcode was used for detecting the highly interacting gene and protein clusters. Moreover, some other plugin of Cytoscape, like MIME, Vistaclara, Network analyzer were used for getting more information on the interactions.
Results
The protein-protein interaction network related to Sirtuin family has been analyzed. SIRT1 is resulted to interact with many proteins and to form complexes with p53, PCAF/MYOD, PGC1a, HIV TAT, MEF2D, HDAC4, p300, SIRT2, FOXO3 etc. The evaluation of the average clustering coefficient distribution gives the average of the clustering coefficients for all nodes n with k neighbors and identifies a modular organization of metabolic networks. The clustering coefficient of whole network of SIRT1 is resulted equal to 0.632 indicating that this SIRT1 can be inferred as hub protein. We are also analyzing the presence of SIRT1 in some different pathways. In particular, analyzing the signaling mediated by HDAC class 1 network, SIRT1 is found to have high values of centralities in this network indicating that it is an important protein in HDAC Signaling events. Interestingly, SIRT1 is found to be interacting as 2nd order neighbor with many proteins like Tubulin, Cytoplasmic Dyneins, Dynactin, Tubulin and LRRK, Adiponectin which are expressed in neurodegenerative diseases. This indicates that indirect or dependent interactions can also be regulating the gene and protein functions associated or interacting with SIRT1.

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