Reconstruction and analysis of the NF-kB pathway interactomr

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Motivation

One of the phenomena observed in human aging is the progressive increase of a systemic inflammatory state (cit), a condition referred to as “inflammaging” (cit), negatively correlated with longevity (cit). A prominent mediator of inflammation is the transcription factor NF-kB, that acts as key transcriptional regulator of many genes coding for pro-inflammatory cytokines. Many different signaling pathways activated by very diverse stimuli converge on NF-kB, resulting in a regulatory system characterized by high complexity. Scope of this analysis is to provide a wider, systemic picture of such intricate signaling system.

Methods

The authors followed a workflow for gathering information from literature as well as from several pathway and protein interactions databases, and for integrating and analyzing existing data and the relative reconstructed representations by using the available computational tools (cit mio). Strong manual intervention has been necessarily used to integrate data from multiple sources into a single object. The reconstruction of the NF-kB interactome pursued with this approach provides a starting point for a general view of the architecture and analysis of this complex regulatory system.

Results

A “core” and a “wider” NF-kB pathway interactome, consisting of 140 and 3146 proteins respectively, were reconstructed. Among other features, the topological characterization of the interactomes shows that a relevant number of interacting proteins are in turn products of genes that are controlled and regulated in their expression exactly by NF-kB transcription factors. These “feedback loops”not always intuitive, deserve deeper investigation since they could have a role in tuning the response and the output consequent to NF-kB pathway initiation, in regulating the intensity of the response, or its homeostasis and balance in order to make the functioning of such critical system more robust and reliable. This integrated view suggests that NF-kB transcription factors family and their direct interacting proteins are at the core of a so-called “bow-tie” structure, where the fan in is constituted by the large variety of activator signals from cell surface receptors, and the fan out is

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represented by the high number of downstream genes and the corresponding cell responses and phenotypes.

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