Genome-Wide Survey of mixed MicroRNA / Transcription Factor Feed-Forward Regulatory Circuits in Human

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Motivation

A basic notion of modern system biology is that biological functions are performed by groups of genes which act in an interdependent and synergic way. This is true in particular for regulatory processes for which it is by now mandatory to assume a “network” point of view. Among the various important consequences of this approach a prominent role is played by the notion of “network motif”. The idea is that a complex network (say a regulatory network) can be divided into simpler, distinct regulatory patterns called network motifs, typically composed by three or four interacting components which are able to perform elementary signal processing functions. Network motifs can be thought of as the smallest functional modules of the network and, by suitably combining them, the whole complexity of the original network can be recovered. Usually, in higher eukaryotes, gene regulation is primary linked to the action of promoters and 3’-UTRs that are thought to control the expression of coding genes mainly in response to transcription factors (TF) and microRNAs. In particular, several methods exist to elucidate TF-related and microRNA-related regulatory networks, but comparable information is lacking to explicitly connect them.

Methods

In this talk, we report the results of a genome-wide integration study of a transcriptional and post-transcriptional regulatory network, in human, based on a bioinformatic sequence-analysis work. In particular, we focused in the study of functional and statistical properties of a special class of network motifs, the mixed TF/microRNA feed-forward circuits, recently proved to be of significant importance. A human genome-wide catalogue of this type of circuits was assembled with a two step procedure. We first constructed a transcriptional regulatory network and, separately, a list of post-transcriptionally regulated genes for human by looking for conserved overrepresented motifs in human and mouse promoters and 3’-UTRs. Second we combined the two datasets looking for mixed feed-forward regulatory loops (FFLs), i.e. all the possible instances in which a master transcription factor regulates a microRNA and together with it a set of joint target coding genes. We obtained a catalogue composed by a total of a few hundreds of such regulatory circuits in human. In order to investigate the biological relevance of these interactions we then filtered the proposed catalogue of mixed FFLs using three selection criteria:
I) Gene Ontology enrichment among the joint targets of the FFL.
II) Gene Ontology similarity between the TF governing the circuit and the joint targets
III) Independent computational evidence for the regulatory interactions of the FFL, extracted from the ECRbase, miRBase, PicTar and TargetScan databases.
IV) Relevance to cancer of the FFL as deduced from their intersection with the Oncomir and Cancer Gene Census databases.

Results

Several biologically relevant circuits were recognized and discussed, describing in particular aspects of organism development and differentiation. In a few cases some (or all) of the regulatory interactions which composed the mixed FFL were found to be already known in the literature, with their interplay in a closed regulatory circuit not noticed, thus representing an important validation of our approach. However for several loops we predicted new regulatory interactions, which represent reliable targets for experimental validation. Among the various loops that we found we finally describe with particular attention circuits with potential involvement in cancer. In parallel to that, the properties of the proposed mixed FFLs in terms of network motifs where investigated through extensive use of randomization procedures applied to the transcriptional and post-transcriptional networks. We show that such FFLs occur more frequently in the real human regulatory network than expected by chance and, hence, can be considered as a genuine network motif. In conclusion, we conducted a bioinformatic investigation aimed at

the systematic integration of transcriptional and post-transcriptional regulatory interactions, in the human genome. As final outcome, we report a catalogue of mixed (transcription factor / microRNA) feed-forward regulatory circuits and we discuss their possible biological importance and properties.

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