Theoretical approaches to understand gene regulatory networks that sustain angiogenesis in tumor and chronic diseases.

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Background

The process of angiogenesis implements the formation of the vascular network by generating new blood vessels from the pre-existing ones and play an important role during development and in several pathological settings. Angiogenesis is a challenging area in molecular medicine, since therapeutic opportunities based on antiangiogenic regimens are now available, mainly in the area of oncology and in ophthalmology. However, clinical experience has indicated that the effects of anti-vascular compounds are often transient or even negligible, with patients displaying intrinsic or acquired resistance. Current strategies employed to tackle angiogenesis are largely based on previous reductionist studies mainly designed to identify the roles of ligand-receptor pairs. However, **the complexity of the angiogenic process requires new approaches to decipher the properties of the signaling networks within the cells.** In fact, angiogenesis is a multistep process sustained by an orchestrated control of many cellular functions, including activation of quiescent endothelial cells by an angiogenic inducer, basal lamina and extracellular matrix degradation, cell migration, and cell proliferation. In addition, endothelial cell metabolism has recently been described as essential angiogenic driver. **At the gene expression level, coordination of these cellular activities is precisely controlled through multiple layers of regulation**, both at transcriptional and post-transcriptional level, where non-coding RNAs play an important role that is still far to be elucidated.

Our recent research activity

To fully capture the phenotypic changes occurring to endothelial cells during angiogenesis in its complexity, beyond the reductionist approach, we recently exploited a three-dimensional cell culture model that *in vitro* recapitulates the angiogenic program. RNA Sequencing technology was employed to annotate all the protein-coding genes, microRNAs and long non-coding RNA that are expressed in this experimental model and to measure alterations in their expression level. By developing a specific bioinformatics pipeline that combines co-expression analysis, microRNA target prediction and network analysis, we were able to **estimate the impact of microRNAs activity on the many biological functions that are activated during angiogenesis.** This approach allowed the identification of interactions that more likely are affected by the post-transcriptional regulation layer together with the identification of new genes to be considered for subsequent validation in tissues from colorectal cancer patients and to be exploited for targeted therapies.

The research project

To develop a new level of understanding of the angiogenic process, we intend to implement our **mixed approach based on network theory and expression data generated in our lab** in several ways: 1) by annotating the recurrent motifs that defines quiescent endothelial cells compared to activated ones and the role that transcription factors plays in the rewiring of the transcriptional network induced by an angiogenic stimulus; 2) by integrating in the regulatory network, as interconnected variable, the activity of long non-coding RNAs, an emerging class of regulatory RNAs still poorly characterized; 3) by developing new computational and bioinformatics tools to analyze the response/adaptation of endothelial cells challenged in models that include also cancer cells.

The student involved in this project will be flanked by a wet biologist. His activities will be devoted to data analysis and to the development of bioinformatics tools aimed to 1) the identification of functional interactions among protein-coding genes, microRNAs and long non-coding RNAs; 2) the generation and analysis of complex networks; 3) the prediction of outcome after system perturbations; 4) the identification of relevant biological targets.

Research activities will be conducted at the Department of Oncology of the University of Turin, which is located at the Istituto di Candiolo – IRCCS, Candiolo (TO), Italy.

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Research Project: Network Theory for Gene Regulation

A basic notion of modern system biology is that biological functions are performed by groups of genes which act in an interdependent and synergistic way.
Network structures appear in molecular biology at several levels, from the description of protein-protein interactions, to the organization of relevant chemical reactions into metabolic networks, to the study of regulatory processes.
The aim of this project is to use methods and ideas borrowed from network theory to combine these different layers of information and use them to identify and study relevant regulatory and signaling pathways both in healthy and pathological tissues. In particular one of the main goals of the project will be the identification, using these methods, of cancer driver genes.

The project is based on three main ingredients of network theory:
- first the idea of "**network motif**" which plays a prominent role in modern applications of network theory to systems biology. The idea is that complex biological networks (say the regulatory network) can be divided into simpler, distinct regulatory patterns called network motifs, composed by few interacting components which are able to perform elementary signal processing functions.
- second the combination of different layers of information in the so called "**Multplex networks**" in which the nodes (typically the genes) are linked by different layers of relations. Multiplex networks are one of the most advanced directions of network theory and are certainly the best tool to encode the interactions among the different links joining a pair of genes and the biological information they encode.
- third the identification within the multiplex of clusters (or more precisely "**communities**") of genes which are more densely connected among them than with the other nodes of the networks and are thus likely to be involved in some common pathway or biological function.

From a biological point of view the main innovation of our project will be the special attention which we plan to devote to the post-transcriptional layer of regulation and to its interplay with the epigenetic layer of regulation.

As a result of our project we will identify sets of candidate driver genes for the pathology of interest. In particular we plan to optimize our analysis for the identification of cancer driver genes. The final goal of the project is to integrate our efforts with those of our wet biology colleagues, with whom there is a long standing record of fruitful collaboration, toward the definition of new network-based strategies for the so called "personalized medicine" approach to cancer therapy.

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STUDY OF COMPLEX CURRENT ENVIRONMENTAL PROBLEMS

The project aims at formulating mathematical models for solving 2 important environmental problems:
(1) the disappearance of pollinator insects;
(2) use of fungi for wastewater treatment.

(1)

Objectives:
to build a model to predict Varroa infestation in beehives
and to fight it, reducing the use of pesticides.

Methodology:

Bees are the most important pollinators, thus they are fundamental for agriculture and life on Earth.
They are used to produce honey, wax and royal jelly, but are endangered due to anthropic causes, as
the use of insecticides, or natural, presence of parasites as the Varroa destructor mite.

Some starting models to assess the Varroa impact on beehives
need calibration, using the results of field experiments that are being undertaken.
By suitable simulations we will produce useful information for beekeepers.

(2)

Objectives:

Construction of models for assessing
the optimal configuration of the supports of fungi in the treatment of wastewaters
and the use of fungi in eliminating soil pollution.
We will apply our results in civil and industrial wastewater treatments for various pollutants. The results will be notified to the local municipalities administrators,
as well as to conferences and international scientific journals.

Methodology:

The pollutant in wastewaters is decomposed by bacteria, but experimentally also fungi have been used. Recently models are now calibrated using
laboratory experiments.

We intend to repeat the experiment in large scale, using bioreactors, so as to validate the model and being able to predict the system evolution in time.
Some preliminary results indicate that the reaction can sustain itself without the continuous feeding of fungi, with a sizable economic advantage.

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(http://www.dipmatematica.unito.it/do/docenti.pl/Show?_id=eventuri#profilo)