Quantifying the relevance of different mediators in the human immune cell network

Tieri P (1,2), Valensin S (1,2), Latora V (3), Castellani GC (2), Marchiori M (4,5), Remondini D (2), Franceschi C (1,2,6)

(1) Dipartimento di Patologia Sperimentale, Università di Bologna, Bologna
(2) C.I.G.-Centro Interdipartimentale 'L. Galvani', Università di Bologna, Bologna
(3) Dipartimento di Fisica ed Astronomia & INFN, Università di Catania, Catania
(4) W3C MIT Lab for Computer Science, Cambridge, USA
(5) Dipartimento di Informatica, Università di Venezia, Venezia
(6) INRCA -Istituto Nazionale di Ricovero e Cura Anziani, Ancona

Motivation

The cells of the Immune System (IS) communicate by direct surface contact and indirectly, by means of soluble mediator proteins released and bound by the immune cells. Soluble mediators implement cellular communication both at short range and across the major body systems. The network we consider is constituted by various immune cell types, which can act as both sources and targets of the exchanged mediators. Mediators are characterized by pleiotropy (each mediator has multiple targets) and redundancy (each mediator is produced by several sources), two characteristics that strongly influence the reliability, the robustness and the adaptability of the IS. In this view we built a network of IS cells whose cell-cell interactions are mediated by soluble molecules such as cytokines, chemokines, hormones. From experimental immunological knowledge we have two types of information: 1) each cell type secretes a defined set of mediators; 2) each mediator affects a defined set of cells. Combining information from these two datasets we can write down a complete"relationship matrix" among immune cell types where the relations are constituted by exchanged soluble mediators. Following this approach we retrieved all available literature data from the online Cytokine Reference Database, choosing a set of 19 cell types involved in the most relevant immune processes and the related secreted and affecting mediators (90 proteins).

Methods

The immune cell network is represented as a valued directed graph, cell types are the vertices of the graph and the soluble mediators form its arcs: a directed arc from vertex i to vertex j is defined by the existence of at least one mediator secreted by cell i and affecting cell j. Cell self-stimulation by soluble mediators (autocriny) is also taken into account. The value eij referred to each arc is equal to the number of different mediators connecting the cell i to the cell j. We consider such a number as a measure of the importance of the communication between two cells along the arc, hence modelling this as an efficiency that measures the bandwidth. Two cells/vertices in the graph can communicate through various paths, connecting them with different levels of efficiency. We assume that the communication between vertices i and j takes the most efficient path, the one that assures the widest communication band possible. We characterize the system global properties by defining the network efficiency given by the sum of the most efficient paths that link up every couple of nodes divided by the squared number of the existing nodes. Here we propose a method for quantifying the centrality of the various soluble mediators in the IS. The method is based on the concept of efficient communication over the immune cell network. The centrality of each mediator is measured by its network relevance, defined as the relative drop in the network efficiency caused by the removal of the mediator. In fact, in our framework, the removal of a mediator weakens some of the values eij relative to the arcs and, consequently, affects the communication between various couples of cells, influencing the efficiency of some paths and thus the whole IS network efficiency.

Results

The graph has 19 vertices and 316 arcs that include self-connections, out of the 361 possible arcs, and thus a pure topological analysis would have been poorly significant. Therefore, we performed a more refined analysis by taking into account the strength of the interactions among the IS cells. The integer values eij attached to the arcs range from 1 to 36, since there are up to 36 different mediators

connecting a couple of cells. Three mediators out of 90 only, TGF-b, MIP-1-alpha and -beta, and TNF-a, show a network relevance larger than 0.5; 11 mediators have network relevance in the range [0.2, 0.5]; and, the remaining 76 have network relevance in the range [0, 0.2]. The sum of the network relevance of the first three mediators accounts for the 20.5% of total mediators relevance, while those of the second and third groups account for 27.6% and 51.9%, respectively. The three most important mediators are pro- and anti-inflammatory molecules, and are involved in the communication among a large number of cell types, i.e. in 216, 224 and 120 interactions, respectively. The second group of mediators includes 9 pro- and anti-inflammatory cytokines/chemokines, one non-inflammatory cytokine (IL-7), and one neuro-endocrine hormone (VIP/PACAP). So, notwithstanding the fact that mediators involved in the inflammatory process account only for 24% of all mediators, 86% of the top molecules are inflammatory, accounting for 50% of all inflammatory mediators. In conclusion, mediators involved in innate immunity -the most ancestral branch of the immune system- and in highly conserved defence pathways such as inflammation, appears to give a substantial contribution to the efficient communication of the IS network.

Availability: http://www.immunologia.unibo.it/en/models/models.htm

Contact email: p.tieri@unibo.it