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Quantification of mediator relevance in immune cell network

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The complexity of soluble cell-cell communication network in the human immune system can be approached by means of mathematical modelling and bioinformatics. Studies from our group have proven that the most important cytokines for the communication and connectivity of the immune system (IS) are mainly of pro- or anti-inflammatory type. IS, as well as many other systems, has been methodically analysed as regards to its components and function by using a very successful reductionist approach. Indeed, the overall functioning principles of the IS cannot easily be predicted by studying the properties of its isolated components because they strongly rely on, and arise from, the interactions among these numerous and highly heterogeneous constituents.

Systems biology adds to the traditional study of isolated entities (genes, proteins, cells, and organs) a new perspective that considers biological systems as a whole of components plus the network of their relationships, focusing on the emerging features that cannot be directly inferred from the properties of its individual components [1]. A way to study some aspects of a system is to use mathematical tools as graph theory and thus to consider the elements as parts of a network to be depicted as nodes, interconnected with physical, chemical or functional links, represented by arcs. In this view, the increasing amount of data on metabolic reaction pathways, protein-protein and genome-protein interactions allowed for the building of metabolic, protein-interaction and genetic control networks [2-8].

Several studies have reported that the topology of these biological networks is not accidental, but it has a distinguishing scale-free structure: the distribution of connectivity (i.e. the number of nodes directly linked to each node) is not homogeneous, that is, it does not scale gradually but rather it follows a "power law", where highly connected nodes (hubs) are very few and the majority remaining nodes have low connectivity [9]; on the contrary, random network connectivity follows a

Poisson distribution. Scale-free networks show two main features: a) the pathway between any two nodes is always short because the hubs play as shortcuts, and b) they show tolerance against random elimination of nodes because of the presence of alternative pathways through the hubs.

To cite an example, the analysis carried out by Jeong et al. [4] on the proteome of *Saccaromices Cerevisiae* identified an interaction network with a typical scale-free topology and correlated this structure with the phenotypic effect of their individual removal from the yeast proteome. This study showed that the 1870 proteins linked by 2240 direct physical interactions form a highly heterogeneous scale-free network in which a few highly connected proteins play a central task in mediating interactions among numerous, less connected proteins. As Jeong et al. demonstrate, proteins with five or fewer links constitute about 93% of the total number of proteins, but only about 21% of them are essential (i.e. their deletion is lethal for the cell). On the contrary, only some 0.7% of the investigated yeast proteins have more than 15 links, but single deletion of 62% of these turns out to be lethal. So the authors strongly suggest that highly connected proteins with a central role in the network's architecture are three times more likely to be essential than proteins with only few links to other proteins.

In immunology each cell communicates with other cells through soluble mediators such as cytokines, chemokines and hormones, among others, that are crucial for the functioning of the IS and its fine tuning. From an experimental as well as a theoretical point of view, the main attention has been generally focused on few and very limited subsets of immune cell types and mediators. This has been due to the overwhelming complexity of managing the great variety of signals, their target-differential (different effect on different target) and time-differential (different effect in different time) action performed, their cross-stimulating and cross-interfering activity.

We tried to understand how this wide set of mediators acts and rules the communication among the main IS players [10]. The network we took into account is constituted by various immune cell types (the nodes), which can act as both sources and targets of the exchanged mediators (the arcs). So we built a network of IS cell interactions where these interactions are mediated by soluble molecules such as cytokines, chemokines and hormones. In this view each mediator can contribute with a fraction (or the whole, if it is the only mediator exchanged by two cell types) of "bandwidth" of the information flux between cell types. A part of the network is depicted in Figure 1. Our aim was to quantify the relevance of each mediator in ruling out the communication among cell types of the IS. In other words we wanted to know how much the efficiency of the communication within the cell network would have been affected by the removal of a single mediator. In fact, deletion of a mediator in a key position, that results for example in halving or interrupting the flux of information between two cell types, clearly results much more relevant than deletion of a mediator that, being positioned in a minor topological site, reduces the information flux of a fraction only.

Once defined the set of IS cells and mediators (19 and 90 respectively) and applied the method for computing the weight of the mediators in the network of intercommunicating cells [10], we observed a substantial inequality of the mediator relevance: the three most important mediators are pro- and anti-inflammatory molecules, TGF-β, MIP-1- α /β and TNF- α. This is due in part to the fact that they are involved in the communication between a large number of cell type interactions,

i.e. in 216, 224 and 120 interactions, respectively (being 19 the cell types considered, thus 19×19=361 is the maximum number of possible interactions, self interactions included) but mainly to their topological position. It is worthy to be noted that notwithstanding the fact that mediators involved in the inflammatory process account only for 24% of all mediators, 86% (twelve out of fourteen) of the top molecules are inflammatory, accounting for 50% of all inflammatory mediators. In synthesis our analysis showed that mediators involved in innate immunity and inflammation have the most central role in the immune network. So, the indication that innate immunity and inflammation are related to survival at extreme ages [11,12,13] or conversely mortality caused by major age-associated diseases (low or high level of inflammation, respectively) is reinforced by this study that indicates that mediators involved in such ancestral branch of the IS and in highly conserved defence pathways such as inflammation, appear to give a substantial contribution to the efficient communication of the IS network.

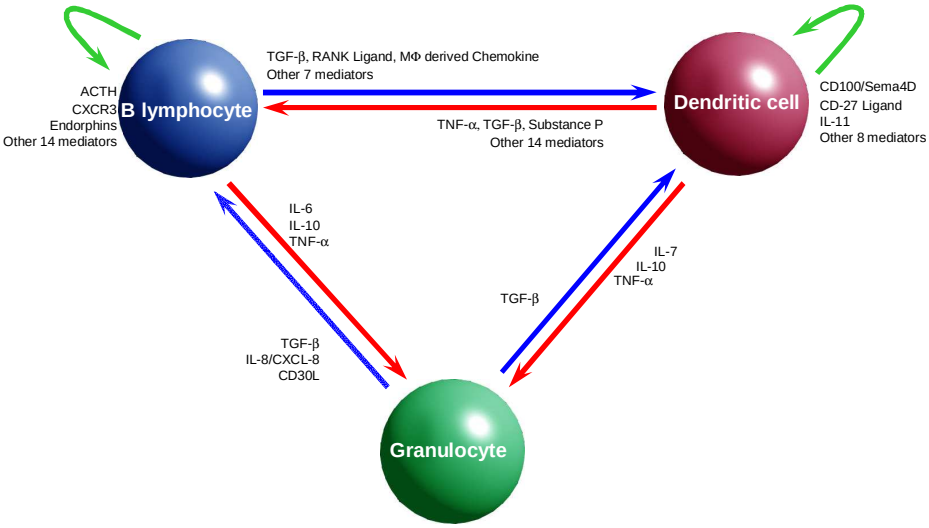

Fig. 1 Portion of the immune cell network considered in [10]. A network with only three out of 19 cell types considered in the paper is illustrated. Cell types are the nodes of the graph, while diffusible mediators (cytokines), which enable the cells to communicate each other, define the arcs of the graph. Autocriny is also considered and depicted in the figure. The names of the mediators are listed close to the respective arcs. It is clear how, in this example, the information flux is heavily affected by the removal of TGF-β. Such removal would indeed completely interrupt the informative flow between granulocytes and dendritic cells and reduce the bandwidth of informative flow among the other cell types.

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