CANINE LEISHMANIASIS AND BIOLOGICAL NETWORKS: A NEW APPROACH FOR AN OLD PROBLEM

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Purpose of the work. *Leishmaniasis is a widespread parasitic zoonoses[1] which affect human and few other mammals including dogs and cats[2,3]. Canids are the main reservoirs for the viscerotropic species in the Mediterranean, Asia, North Africa and South America1. Leishmaniasis represents indeed a serious problem for human health, with enormous social costs[1,4,5]. Despite the amazing efforts of scientific community, to date, really effective therapeutical resources are not still available. This could not be due to the scarcity of molecular data, but to the inability to manage them in explicative models. Thus, for the first time, we have adopted a very innovative biological networks-based approach to describe the relationship between the parasite and the host. In particular, we described the recognition, binding and phagocytosis of Leishmania amastigote by monocyte as a network composed by nodes (molecules involved) linked by edges (their interaction). Then, we carried out a statistical analysis of network's topology to obtain significative biological inference.*

Materials and used methods. *We downloaded the data from KEGG Pathways Menu (http://www.genome.jp/kegg-bin/show_pathway? org_name=cfa&mapno=05140&mapscale=1.0&show_description=show), filtering the data for Canis familiaris, pathway ID: cfa05140. The network (Leishmania Host Interaction Network, LHIN) was created and analysed by Cytoscape 2.8.3 and Network Analyzer, and was classified on the basis of its topological parameters. Actually, it is possible to classify biological networks in different typologies according to these parameters. The most elementary characteristic are the node degree, k, indicatig how many links the node has to other nodes, and the node degree distribution, P(k), which represents the probability that*

a node has exactly k links. The network tendency to develop clusters of nodes is expressed by the clustering coefficient CI = 2nI/k(k–1), where nI is the number of links connecting the kI neighbours of node I to each other. In random networks, described by the Erdös–Rényi (ER)[6] model, the node degrees follows a Poisson distribution and the clustering coefficient is independent by nodes degree. Scale-free networks (Barabási–Albert, BA, model)[7] are characterized by a power-law degree distribution of the number of links per node. Thus, a relatively small number of nodes is highly connected (hubs) and most of the nodes are scarcely linked. In addition, the clustering coefficient is independent by the number of links per node. In the hierarchical networks the scale-free topology and the local clustering coexist.

Outcomes. *We have found that LHIN is composed by 74 nodes and 85 edges. The clustering coefficient was 0.018, the network diameter (i.e., the largest distance between two nodes) was 8, the characteristic path length (i.e., the expected distance between two connected nodes) was 3.088, the averaged number of neighbours (i.e., the mean number of connections of each node) was 2.297. The most connected nodes were: nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) extracellular-signal-regulated kinases (ERK1/2) and protein kinase C (PKC), each 6 links; inducible nitric oxide synthases (iNOS) gene and lipophosphoglycan (LPG), each 5 links. The LHIN displayed two important characteristics:*

- it is a random network, according to ER model;

- it is a directed network, having an input and an output terminal.

Conclusions. *In our opinion, few conclusions can be drawn from these findings. The first could justify the failure of development of anti-leishmania drugs. Indeed, random networks, differently from scale-free networks, are highly resilient to attack (removal of most connected nodes)[8], consequently, it is very hard to destroy LHIN with a targeted drug therapy, as confirmed by a computer simulation in which the removal of the most connected nodes did not significatively affected the main topological indexes.*

Secondly, since an attack strategy seems to be not effective, the only remaining way to destroy LHIN is to stop the flow of molecular event through the network. As strengthened by networks topology, LPG appears to be one of the most connected nodes and, contemporaneously, it is the network input terminal. As a consequence, LPG seems to be a favourable target for drugs development against Leishmania. Interestingly LPG is described in literature as the main responsible for the macrophages phagolysosome maturation inhibitions[9,10,11] and in human Leishmania major LPG1- mutants show attenuated virulence when compared with the wild type[12,13].

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