Critical points in a pathogen bacterial network and their implication for drug discovery.

ID - 225

Loguercio Salvatore[1]

[1]Department of Biological sciences-Biostructures section- University of Naples 'Federico II', Napoli

Motivation

Complex systems such as living cells have a 'robust yet fragile' feature, in which robustness in response to certain perturbation is inevitably associated with fragility in response to other perturbations (Kitano, Nat Rev Drug Discov., 2007).

Finding the points of fragility of the pathogenic microbial cells is a key issue in antibacterial drug discovery. Here we describe a general approach to identify control points in a microbial molecular network, which could be targets for novel drugs. The strategy is implemented on Helicobacter pylori 26695, an human gastric pathogen infecting almost half of the world population (Beswick et al., World J Gastroenterol., 2006). The entire metabolic network of the pathogen is screened to find biochemically critical points, e.g. enzymes which uniquely consume and/or produce a certain metabolite (Rahman and Schomburg, Bioinformatics, 2006). A comparative study between the identified bacterial critical points and the known essential genes for H.pylori was performed. Enzymes acting as critical points in the human biochemical network as well as in the pathogen network were removed. Further selections were made on results obtained by performing a homology search against the human genome. Finally, the essentiality of the identified targets is cross-validated by in silico deletion studies on a recent genome-scale metabolic model of H.pylori.

Methods

We consider a reconstructed metabolic network (enzymes/metabolites) of Helicobacter Pylori 26695, built using the LIGAND (Goto et al, Nucleic Acids Res., 2002) database from KEGG (Kanehisa et al., Nucleic Acids Res., 2004) and the BRENDA enzyme database (Schomburg et al., Nucleic Acids Res., 2004). We used the Pathway Hunter algorithm (Rahman et al., Bioinformatics, 2005) to estimate and rank the bio-chemically critical points in the network. A database of essential genes was built using data from single knockout experiments and from global transposon mutagenesis (Salama et al., J. Bacteriol., 2004; Baldwin et al., J. Bacteriol., 2006). The homology search between the human and H.pylori enzymes was executed using BLAST and enzymes with a closest homologue with e-values < 1.0e-02 were removed. In silico deletion studies were performed using costraint-based reconstruction and analysis (COBRA tecnique: Palsson et al., Nat Methods, 2007) on the H.pylori iIT341 GSM/GPR in silico metabolic model (Thiele et al., J. Bacteriol., 2005).

Results

The strategy was implemented on the pathogen bacterial network of Helicobacter pylori strain 26695. Potential drug targets are proposed based on the analysis of the top 20 critical points in the bacterial network. These enzymes are compared to the essential genes for H. pylori identified from biomedical literature, in order to extract consensus targets for the bacterium's survival and pathogenicity. Once identified, the list of potential targets is filtered in two steps. First, a comparative study was performed between the human metabolic network and pathogen critical points to discriminate common critical enzymes. A homology search was then performed against human genome to find non-homologus potential drug targets from the pathogen critical points. Finally, a simulation of growth phenotypes resulting from single and double deletion of target enzymes was carried out on a recent genome-scale metabolic reconstruction of H.pylori, in order to cross-validate the essentiality of selected candidates.

Email: loguerci@chemistry.unina.it