Available online at www.sciencedirect.com
ScienceDirect
Infection, Genetics and Evolution xxx (2008) xxx–xxx
Infection, Genetics and Evolution
www.elsevier.com/locate/meegid

Discussion

Potential and limits of *in silico* target discovery—Case study of the search for new antimalarial chemotherapeutic targets

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Received 16 October 2007; accepted 5 January 2008

Abstract

In medical sciences, a *target* is a broad concept to qualify a biological entity and/or a biological phenomenon, on which one aims to act as part of a therapy. It follows that a *target* can be defined as a phenotype, a biological process, a subcellular organelle, a protein or a protein domain. It also follows that a target cannot be defined independently of the type of intervention one considers implementing. In this brief review, we describe how *in silico* organization of genomic and post-genomic information of all partners involved in malaria (human patient, *Plasmodium* parasite and *Anopheles* vector), complying with knowledge of the disease in etiologic terms, appears as an efficient source of information not only to help selecting but also discarding target candidates. Some limitations in our capacity to explore the stored biological information, due to the current quality of genomic annotation, level of database integration, or to the performances of existing analytic and mining tools, are discussed. *In silico* strategies to assess the feasibility of bringing a target to a therapeutic development pipeline, in terms of target ''druggability'', are introduced.

Keywords: Malaria; *Plasmodium*; *Anopheles*; Drug discovery; Chemotherapy; Bioinformatics; Chemogenomics; Druggable genome

1. Introduction

In medical sciences, a *target* is a broad concept to qualify a biological entity and/or a biological phenomenon, on which one aims to act as part of a therapy. It follows that a *target* can be defined as:

- a phenotype (*e.g.* in clinical medicine, symptoms of a disease);
- a biological process (*e.g.* a vital metabolic pathway in a pathogen);
- a subcellular organelle (*e.g.* a vital organelle of a pathogen);
- a protein (*e.g.* a vital protein of a pathogen);
- a protein domain (*e.g.* in structural biology, a pocket at the surface of a protein on which an active drug can dock; numerous targets can be defined on a given protein structure).

It also follows that a target cannot be defined independently of the type of intervention one considers implementing. Intervention depends on the level of knowledge of the disease and the cultural background of the practitioner. Schematically: traditional medicine attempts to oppose the symptoms; allopathic or orthodox medicine attempts to oppose the causes (*i.e.* the etiology) of the diseases; homeopathic medicine, meant as non-allopathic medicine, treats likes with likes (in the widest sense, and irrespective of the dilution principle, vaccination is a category of homeopathic treatment). Intervention also relies on the availability of methods to design and introduce exogenous chemicals (biological extracts and natural substances, drugs purified from biological material or obtained by synthetic chemistry, vaccines) or exogenous genes (gene therapy).

As a result, reviewing the *in silico* strategies for target discovery, characterizations, validations, etc. should be preceded by a definition on what is meant by a target. Here, *targets* will be discussed following their understanding in allopathic medicine, as molecular entities (genes, proteins, protein domains) or biological phenomena (molecular functions, pathways, phenotypes) organized in causal schemes (essentially the DNA → RNA → protein ↔ function/phenotype simplified scheme).

Since a decade, access to complete genomic sequences of human and pathogens has brought the hope that target genes would be rationally identified, allowing the design of new

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doi:10.1016/j.meegid.2008.01.001