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Network, nodes and nexus: systems approach to multitarget therapeutics

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Systems biology is revealing multiple layers of regulatory networks that manifest spatiotemporal variations. Since genes and environment also influence the emergent property of a cell, the biological output requires dynamic understanding of various molecular circuitries. The metabolic networks continually adapt and evolve to cope with the changing milieu of the system, which could also include infection by another organism. Such perturbations of the functional networks can result in disease phenotypes, for instance tuberculosis and cancer. In order to develop effective therapeutics, it is important to determine the disease progression profiles of complex disorders that can reveal dynamic aspects and to develop mutitarget systemic therapies that can help overcome pathway adaptations and redundancy.

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Introduction

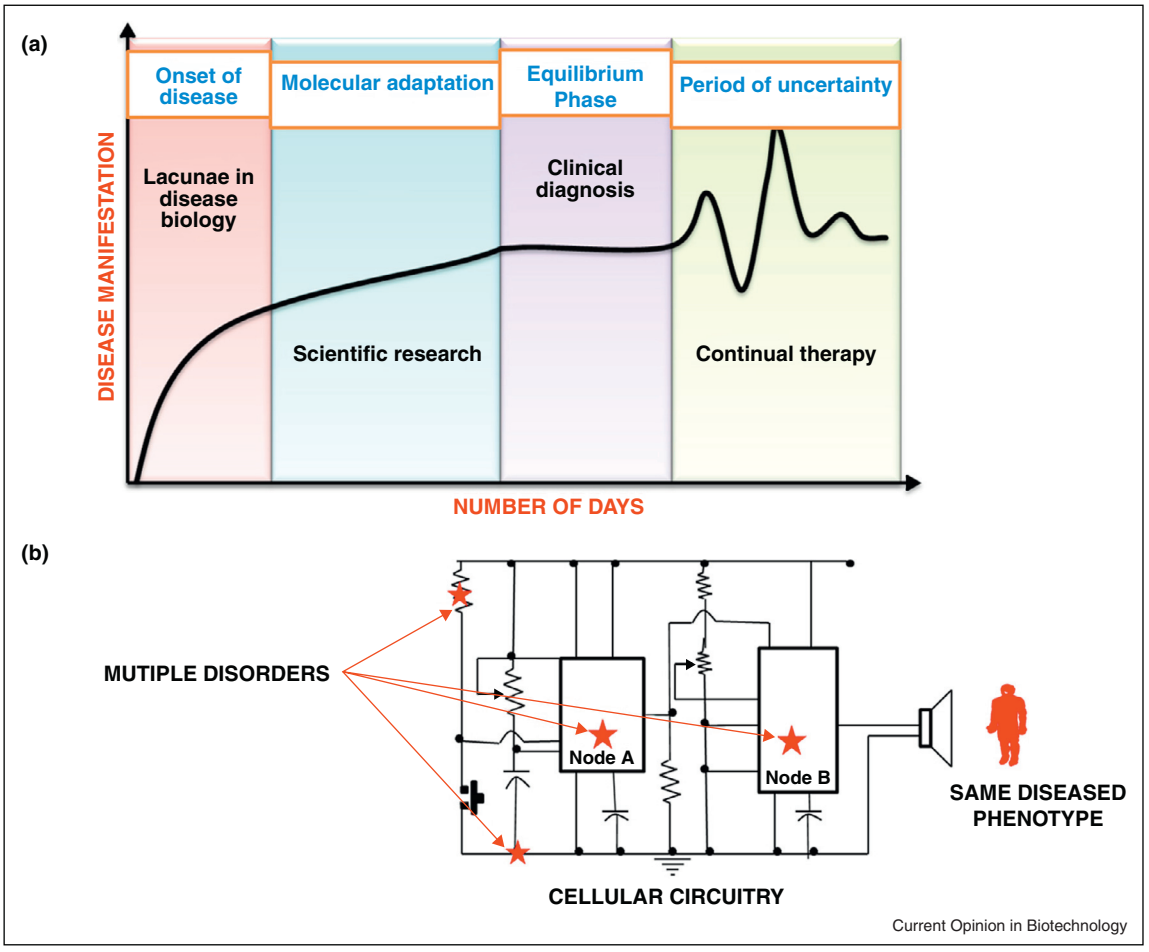
The drug discovery process has been undergoing a succession of interesting paradigm shifts during different periods of human evolution. While ancient practices of medicine followed holistic approaches through careful interpretations, the discovery of antimicrobial agents during the beginning of modern biology era resulted through serendipitous observations [1]. The next wave was spurred by understanding of biological dogmas with emphasis on enzyme functions and specificity of biomolecular interactions. Concurrent increase in the understanding of the mechanisms of drug action along with rapidly developing combinatorial chemistry encouraged the emergence of target-based approaches for drug discovery. The amalgamation of small molecule assemblages and high-throughput screening resulted in an incredible growth in compound statistics [2–4]. However, the benefits from these initiatives have been limited and there has been an escalation in the cost of new molecular entities at an annual rate of approximately 13.4% [5]. Although factors such as design of clinical trials and economic decisions do add to the complexity of drug discovery development, there is also an implicit need to rewire the innovation programs based on systems-level understanding of biological processes.

The advancement in acquiring high throughput data in conjunction with heuristic network algorithms and incredible imaging technologies is resetting many paradigms of biological functionality. The remarkable flexibility and redundancy that is being elucidated in cellular circuitry implies that biology capitalizes survivability by exploiting adaptability rather than utilizing the most efficient systems. It appears that selectivity and specificity in the output of biological function is built-in through multiple layers of sieve, many of which could have interactions of low affinities and even low selectivity. Here we discuss new approaches and strategies of systems biology that could be applied to drug discovery programs. We discuss how understanding of metabolic network-based study can delineate critical nodes and how multitargeting could be rationally developed to generate new classes of 'systemic' drugs.

Lacunae in understanding progression of complex diseases

Complex disorders are multifactorial or polygenic disorders whose outcomes could simultaneously involve multiple perturbations. These phenotypes are further complicated by lifestyle and environmental factors. Although complex disorders often cluster in families, there is no predictable pattern of inheritance. The robustness of biological system that maximizes survival ensues different downstream outcomes making it even harder to determine the trigger. The challenge in unraveling such complexity, therefore, is to define 'Disease progression profiles' (DPPs) as shown in Figure 1a. While the trigger initiates a cascade of cellular events that lead to onset of disease (Phase I), the clinical diagnosis as well as disease management primarily happens during the equilibrium phase (Phase III). Much of the scientific research with model systems is primarily performed in the time frame that is somewhere between these two states (Phase II). The challenge is to establish correlations between resultant phenotypes and various dynamic interacting constituents. An interesting example of a complex disorder

Figure 1



(a) Schematic representation of disease progression profile (DPP) for complex disorders. DPP illustrates disease progression phases underlying complex disorders and the existing lacunae in understanding triggers leading to disease manifestation. **(b)** The electronic circuit and ICs are analogous to biological networks and nodes, respectively. Perturbation of multiple nodes (depicted by red star) leads to a nonfunctional biological circuit and subsequently the same diseased phenotype.

is vitiligo, the manifestation of which could be visually followed during the course of the disease. This depigmenting disorder is characterized by a patchy loss of skin pigment melanin, which is often symmetrical. However, localized as well as acrofacial manifestation can also be observed. The expansion and contraction of these patches due to loss of melanocytes is often unpredictable. Different etiologies such as autoimmune theory, cytotoxic metabolite theory, neural theory, genetic theory and a doctrine of convergence encompassing all factors have been proposed to explain this enigmatic disorder [6]. Genome-wide association (GWA) studies have suggested involvement of 13 susceptibility loci associated with generalized vitiligo [7], while the human leukocyte antigen (HLA)-association study in North Indian and Gujarat population revealed two specific alleles, HLA-B*44:03, and HLA-DRB1*07:01 to be significantly increased in vitiligo patients [8•]. The current treatment regimen also emphasizes on autoimmune disorder and is largely symptomatic with minimal success [9]. It can be argued that complex diseases like vitiligo denote multiple disorders resulting in same phenotype. The loss of pigmentation in the epidermis is a common final outcome that could commence at any of the nodes (represented by integrated circuit, IC) in the metabolic circuit (Figure 1b). The challenge, however, is to identify various fuses that trip the homeostatic circuit manifesting into disease.

Since the research activity in the area of vitiligo is limited, in this review we focus on two most significant complex diseases, tuberculosis (TB) and cancer. We discuss various facets of systems-based understanding and its correlation to remodeling of metabolic networks that could direct future drug discovery processes. Despite the innate differences in their etiopathology both disorders undergo a myriad of adaptations to thrive in the changing milieu