
Cytomics Column

Human Cytome Project, Cytomics, and Systems Biology: The Incentive for New Horizons in Cytometry

Günter Valet*

Max-Planck-Institut für Biochemie, Martinsried, Germany

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SYSTEMS BIOLOGY

Systems biology aims at the quantification of molecular elements and their interrelations in biological systems in response to perturbation to integrate the variety of information into mathematical network models and to correctly predict biological system response to stimuli (1-4).

Although promising for single-cell systems such as bacteria, yeast, or cell cultures, difficulties arise for complex mammalian organisms with numerous genes, diversity of genotypes among individuals, and variable exposure histories to environmental influences. Additional complexity derives from the diversity of organs and specialized tissues, each consisting of multiple cell types of significant internal heterogeneity, e.g. of cell cycle, functional status, size, and molecule content.

Cell cultures or diseased and genetically modified animals may in certain circumstances serve as model systems for human disease. However, significant concerns as to the ultimate validity of the conclusions from such model systems for the human *in vivo* situation, especially in disease, or in the search for new drug targets have been raised (5). Cell or animal model systems may ultimately not permit one to generate valid mathematical models of the human organism by systems biology, permitting, e.g., the accurate prediction of a particular patient's reaction to stimuli such as microbial infection, interaction with toxic substances, or adverse drug reactions from mathematical network models.

It is also questionable whether a preexisting mathematical model for an entire biological system such as the human organism represents a prerequisite for the understanding and mathematical modeling of specific molecular disease pathways in complex diseases such as cancer, allergies, rheumatoid arthritis, asthma, diabetes, or infections.

MOLECULAR CELL PHENOTYPING BY CYTOMICS

The analysis of molecular cell phenotypes by cytomics (6,7) represents a simplifying strategy for the dissection of molecular disease networks. Differential molecular screens of single cells from diseased versus reference persons in disease-associated cell systems provide discriminatory data patterns or biomarker patterns for predictive medicine by cytomics and for the detection of new drug targets (8,9) by using hypothesis-driven selection of screening parameters. Reference persons can be healthy individuals or stationary status or survivor patients. The differentially obtained discriminatory data patterns from cells represent important entry points for molecular reverse engineering by biomedical cell systems biology (7). The reasons for this are that diseases are caused by molecular perturbations in cells and cells represent the elementary construction and function units of cellular systems, organs, and organisms.

Reverse engineering of biological complexity (10) using discriminatory data patterns from patients (8) has the potential to directly elaborate mathematically modeled molecular disease pathways without exact knowledge about the normal condition or the disease-causing mechanisms. Therefore, analysis of molecular differentials in disease circumvents a priori mathematical modeling of systematically perturbed biological systems.

An important advantage for the molecular cell phenotype screening concept consists of the plethora of avail-

*Correspondence to: Günter Valet, Max-Planck-Institut für Biochemie, Cell Biochemistry Laboratory, Martinsried D-82152, Germany.

E-mail: valet@biochem.mpg.de

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able multiparametric data from research or routine diagnostics in large clinical patient cohorts including recent proposals of extended data storage standards (11) for cytometry and image analysis to establish public databases.

HUMAN CYTOME PROJECT

The general applicability of differential molecular cell phenotype screening in disease favors accurate diagnostics and individualized disease course predictions for optimized patient therapy (personalized medicine) and the search for new drug targets.

Therapies are typically applied according to the prognostic reactivity of large patient groups in double-blind studies, mostly stratified by Kaplan-Meier statistics using patterns of clinical and molecular parameters to maximize the fraction of responder patients. However, a significant fraction of the stratified patients usually does not adequately respond to therapy (12). This may reflect inadequate therapy and/or adverse drug reactions causing potential harm and economic waste.

The proposed top-down differential molecular cell phenotype screening has the potential to improve the efficacy of the general health system through more specific diagnostics and individualized patient therapy within stratified patient groups. Considering this potential, the establishment of a dedicated research effort (13–15) in the form of a specifically allocated human cytome project has been proposed (16). The human cytome project is conceived as a joint cross-disciplinary effort of cytomics, systems biology, and high-throughput-oriented research involving basic, clinical, and industry scientists.

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