Editorial

Cytomics in Predictive Medicine

Patient-specific, disease-course predictions with >95% or >99% accuracy during therapy would be highly valuable for everyday medicine. If these predictors were available, disease aggravation or progression, frequently accompanied by irreversible tissue damage or therapeutic side effects, could then potentially be avoided by early preventive therapy. The molecular analysis of heterogeneous cellular systems (cytomics) by cytometry in conjunction with pattern-oriented bioinformatic analysis of the multiparametric cytometric and other data provides a promising approach to individualized or personalized medical treatment or disease management. As a consequence, better patient care and new forms of inductive scientific hypothesis development based on the interpretation of predictive data patterns are at reach. Cytometry Part B (Clin. Cytometry) 53B:1–3, 2003. © 2003 Wiley-Liss, Inc.

Key terms: predictive medicine; clinical cytomics; medical bioinformatics

BACKGROUND

Predictive Medicine aims at the detection of changes in a patient's disease state prior to the manifestation of deterioration or improvement of the current status. Such instances may concern, but obviously are not limited to, multiorgan failure in sepsis or noninfectious posttraumatic shock in intensive care (1,2), or the pretherapeutic identification of high-risk patients in cancer cytostatic therapy (3–6). Accurate predictive measures would more effectively guide early antiinfectious or antishock therapy as well as curative chemotherapy in combination with stem-cell transplantation, potentially providing better survival chances for individual patients with concomitant cost containment. Predictive medicine-guided early reduction or cessation of therapy may lower or abrogate potential therapeutic side effects. Other potentially important aspects of predictive medicine concern the recognition of preasthmatic and early rheumatic disease patients as well as the preoperative identification of patients with a tendency for postoperative complications (7) or coronary artery disease patients with an increased tendency for restenosis or other complications (8–10).

Once initiated, one realizes that most of everyday medicine is full of predictive issues. They are present in a variety of severe diseases like cancer, leukemias, rheumatoid diseases, diabetes, and asthma. However, they are also present when considering complex disease syndromes (11) or infections in newborns, pediatric patients (12,13), adults, or elderly patients, as well as bleeding risks during surgery or other affections. In many instances, individualized disease-course predictions for currently envisaged standard therapies would definitely allow early curative interaction by specific therapeutic measures prior to the occurrence of irreversible tissue destructions with its inherent potential to incapacitate, or compromise, the patient in the longer run.

CHALLENGE

The obvious challenge is to define a generalized access to, or method to identify, individualized predictions (14). Cell-oriented analysis is essential in this effort because diseases are characterized by significant deviations from the normal molecular processes in cellular systems or organs. The determination of the molecular phenotype of discrete cell populations by single cell analyses is therefore particularly promising and represents evidence based medicine (EBM) at the cellular level. Molecular cell phenotypes emerge as the result of a patient's genotype and cellular environment including exposure to disease-inducing agents. While the genotype seems most important at first glance, the medical reality indicates that exposure to disease-inducing causes is frequently more important for disease generation than the genetic background. This is exemplified by individuals who are genetically highly susceptible to allergy or rheumatoid arthritis but are unlikely to develop disease without exposure to allergen, while heavy exposure may provoke disease in genetically relatively resistant individuals.

Cytomics

As the cytometric analysis of the cellular heterogeneity in the expression of multiple molecules in the context of cytomes (cellular systems/organs/body), cytomics ac-

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cesses a wealth of information on the molecular cell phenotype of specific diseases. The term cytomics carries a disciplinary aspect as it was coined by molecular botanists (15) in analogy to genomics and proteomics, describing the analyses of the genome, the proteome, and the cytome (http://www.genomicglossaries.com/content/omes.asp). In contrast to the earlier term of system cytometry (16), it is method independent. Members of a number of national and international organizations are involved in cytometric investigations in this area including the European Working Group on Clinical Cell Analysis (EWGCCA, http://www.ewgcca.org), the Clinical Cytometry Society (CCS, http//cytometry.org), and the International Society of Analytical Cytology (ISAC, http://www.isac-net.org), which has presently set a focus on the basic research-oriented cell biology, molecular biology, bio- and nanotechnology aspects of cytomics.

Medical Bioinformatics

The determination of multiparametric individual cell molecular parameters by cytometry, along with multiplex bead assays as well as cell population and single cell-based microarray technologies, generates large amounts of data. However, a major challenge remains to efficiently and effectively extract the relevant predictive medicine parameters. Currently, this information is frequently extracted in a fragmentary way by computer-assisted identification and characterization of a few cell populations or gene clusters of interest. Alternatively, all of the available information can be screened exhaustively by multiparametric clustering (17,18), data mining, or other procedures (19) for diagnostic or prognostic information-using hypothesis-driven analysis strategies. These frequently require mathematical, statistical, or other assumptions that may unintentionally bias the results. Assumption-free algorithmic evaluation concepts like data sieving (14, http://www.biochem.mpg.de/valet/classif1.html) as a bottom-up approach seem of particular interest for the detection of unknown molecular disease mechanisms that are inaccessible to a-priori top-down oriented hypothesis. Following identification of the important predictive data patterns, a major task will still consist of the consensus-driven development of standardized predictive disease classifiers for clinical purposes.

PATIENT GROUPS

The ultimately desired high statistical significance of results for clinical applications is initially in conflict with the search for individual patient-predictive parameters through the collection of large amounts of multiparametric information. A two-phase strategy is therefore appropriate. During the initial pilot phase, the highest number of potentially relevant individual cell measurements in the multiparametric information data set is collected in prospective studies with clinically well-characterized patient groups at an acceptable minimum of statistical stringency such as a significance level of $P<0.05$ or $P<0.10$. The majority of uninformative parameters can be eliminated at this stage by data sieving or multivariate analysis (7,8). In the second phase, the remaining informative parameters for disease-course prediction are analyzed in statistically large patient groups (3,4).

This provides exact numbers for the reliability of individualized disease-course predictions and eliminates pseudoinformative parameters that for random statistical reasons, have slipped into the group of informative parameters during the first phase. Informative parameters may likewise have been lost for random statistical reasons into the group of noninformative parameters during the initial phase. They may, however, be recoverable during the later deductive hypothesis and concept-forming phase from the molecular context of the predictive parameter pattern that was determined during the first phase.

PROGNOSIS AND PREDICTION

The prognostic information contained in selected clinical and molecular parameters in large patient groups is typically utilized for risk and therapy stratification (3). However, the well-recognized problem remains that therapy responders and nonresponders cannot not now, in general, be identified prior to therapy. The potential for pretherapeutic identification of high-risk, nonresponder patients by predictive medicine (4) is therefore of high clinical interest because it helps to provide early therapeutic alternatives for high-risk patients by objective criteria.

PERSONALIZED MEDICINE

Unlike prenatal screening for rare genetic diseases that is restricted to a particularly important phase in human development, the cytomics-oriented approach to predictive medicine provides an entry into personalized or individualized medicine in a more general sense. Based on disease-course predictions at a $>95\%$ or $>99\%$ accuracy level, current standard therapies can be modified by the clinician on objective grounds according to the specific requirement of the individual patient.

Clinical benefits will concern a better direction of diagnostic and therapeutic efforts to patients in need as well as a potential decrease of unwanted side effects by an earlier stop of therapy. Patients who will not respond to a specific therapy can be shifted immediately to alternative therapeutic approaches, thus lowering the risk for therapeutic failure and side effects at simultaneously reduced therapy costs.

ANALYTICAL TECHNIQUES

Predictive medicine is best implemented by cell-based measurements, e.g., by flow or image cytometry. Cell-oriented gene or protein arrays as well as bead arrays for the capture of solute molecules from serum, plasma, urine, or spinal fluid are equally of high value.

The increasing miniaturization of cytometers through semiconductor light sources and laboratory chip technology makes predictive medicine of interest for general, clinical, and ambulant medicine as point-of-care technology.

Like earlier driving forces in the continuously expanding cytometry field, predictive medicine represents a new challenge for clinicians, molecular biologists and cell-oriented bioinformatic scientists in collaboration with industrial instrument and assay development. The contributions in this supplement represent an initial effort into this new direction of cytometry.

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