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Recognizing the "Patient's Phenotype" through Systems Biology

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Editorial

One of the perhaps most awkward results of the Genome Project was that the number of genes is much lower than had been expected and is, in fact, surprisingly similar for very different organisms. It is therefore clear that the biological complexity of organisms is not reflected merely by the number of genes but by the number of physiologically relevant interactions, spanning across different levels as they are not restricted to cell's networks [1,2]. Indeed, there is no linear relationship among genotype and phenotype. Contrary to what has been hold during the last 50 years, along the framework suggested by the seminal experiment performed by Beadle and Tatum [3] in which a simple and univocal correlation was established among gene expression and organism phenotype. Most genotype-phenotype relationships arise from a much higher underlying complexity. Combinations of identical genotypes and nearly identical environments do not always give rise to identical phenotypes. Identical twins, although strikingly similar, nevertheless often exhibit many differences. Likewise, genotypically undistinguishable bacterial or yeast cells grown side-by-side can express different subsets of transcripts and gene products at any given moment. Even straightforward Mendelian traits are not immune to complex genotype-phenotype relationships [4].

The analysis of the dynamical networks interactions among gene products has been proposed in order to overcome those limitations. The interactome is usually thought as the whole set of molecular interactions in a particular cell and the term specifically refers to physical interactions among molecules and genes, generally displayed as graph [5]. In our perspective, the whole set of molecular dynamical patterns and biophysical cues, pertaining both cells and their microenvironment should be considered in making a more reliable dynamical profile of the disease, according to an integrated "physiome" project. Yet, this approach may be inadequate to grasp the overwhelmingly complexity of chronic diseases, like cancer [6].

A new, different strategy involves comprehensive patient-centred integrated care and multi-scale, multi-modal and multi-level systems approaches, indeed. Rather than studying the disease as a cell-based entity, it will take into account the intertwined gene-environment, molecular-biophysical interactions that lead to individual-specific complex phenotypes [7]. It will implement a road map for predictive, preventive, personalized and participatory medicine based on a robust and extensive knowledge management infrastructure that contains individual patient information. Accordingly, Medicine should be viewed as 'systems-based' science requiring both hypothesis-driven and discovery-driven approaches which are thought to cumulate an impressive body of data [8]. The main differences in respect to the classical-hypothesis driven reconstruction of patient/disease phenotype lies on the fact that models currently available are build on an a-priori ontology, whereas the systems-based phenotypes are centred on statistical modelling of all the complex components of cancer onset, persistence and prognosis [9].

Such systemic approach is unbiased by constraints provided by classical hypothesis-driven classifications and may likely improve knowledge of pathogenesis, find new target-based drugs, biomarkers of co-morbidities and of clinical monitoring. In this approach, phenotypes of patients bearing cancer are analyzed in an integrative manner using mathematical and statistical modelling, taking all factors into account, and enabling the translation from the lowest levels of investigation (molecules, cells, tissues) to the highest and even more complexes, represented by physiological and organ functions. Patients Cancer Phenotypes are defined and further analyzed using iterative cycles of modelling and experimental testing. Pathogenetic factors and novel biomarkers are identified combining datasets from genomics, epigenetics, proteomics, transcriptomics, and metabolomics. These parameters will need to be validated and replicated in independent controls, in both *in vitro* and *in vivo* experiments, as well as in prospective patient cohorts. Additionally, using methods used in non-medical complex model systems, it should be possible to monitor 'early warning signals', which predict the state of disease progression, and the occurrence of abrupt phase transitions (slowing down, increase in autocorrelation and variance) [10].

Yet, several concerns still remain about the effectiveness of such a strategy in achieving a clear-cut medical benefit, given that current personalized programs are largely dependent on theoretical assumptions biased by significant gaps in knowledge as well as conceptual, intellectual, and philosophical limitations [4,11,12].

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