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 expressions and biophysical cues, pertaining both cells and their 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 being 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].

References

1. Jablonka E (2012) Epigenetic variations in heredity and evolution. Clin Pharmacol Ther 92: 683–688.
2. Noble D (2013) Physiology is rocking the foundations of evolutionary biology. Exp Physiol 98: 1235–1243.
3. Beadle GW, Tatum EL (1941) Genetic Control of Biochemical Reactions in Neurospora. Proc Natl Acad Sci 27: 499–506.
4. Joyner MJ, Prendergast FG (2014) Chasing Mendel: five questions for personalized medicine. J Physiol 592: 2381–2388.
5. Vidal M, Cusick ME, Barabasi AL (2011) Interactome networks and human disease. Cell 144: 986–998.
6. Sonnenschein C, Davis B, Soto AM (2014) A novel pathogenic classification of cancers. Cancer Cell Int 14: 113.
7. Wolkenhauer O, Auffray C, Brass O, Clairambault J, Deutsch A et al. (2014) Enabling multiscale modeling in systems medicine. Genome Med 6: 21.
8. Hamburg MA, Collins FS (2010) The path to personalized medicine. N Eng J Med 363: 301–304.
9. Bizzarri M, Palombo A, Cucina A (2013) Theoretical aspects of Systems Biology. Prog Biophys Mol Biol 112: 33–43.
10. Li M, Zeng T, Liu R, Chen L (2014) Detecting tissue-specific early warning signals for complex diseases based on dynamical network biomarkers: study of type 2 diabetes by cross-tissue analysis. Brief Bioinform 15: 229-243.

11. Trelles O, Prins P, Snir M, Jansen RC (2011) Big data, but are we ready? Nat Rev Genet 12: 224.

12. Del Bufalo A, Russo P, Milic M, Pristipino C, Fini M, et al. (2014) Systems Biology and Systems Medicine: The Technological Tools of the System Approaches to Complexity. Med chem 4: 473-480.