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Review

Translational genomics

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A B S T R A C T

The term "Translational Genomics" reflects both title and mission of this new journal. "Translational" has traditionally been understood as "applied research" or "development", different from or even opposed to "basic research". Recent scientific and societal developments have triggered a re-assessment of the connotation that "translational" and "basic" are either/or activities: translational research nowadays aims at feeding the best science into applications and solutions for human society. We therefore argue here basic science to be challenged and leveraged for its relevance to human health and societal benefits. This more recent approach and attitude are catalyzed by four trends or developments: evidence-based solutions; large-scale, high dimensional data; consumer/patient empowerment; and systems-level understanding.

Contents

1. Introduction

Translational genomics is both the title and mission of this new journal. Translational research has a long history of practice that was formalized by the creation of the U.S. NIH National Center for Translational Research (Collins, 2011) and the UK's Medical Research Council program in Translational Research (http://tinyurl.com/owmvp4o). Governments throughout the world are funding research programs and centers (e.g., (Daiming et al., 2012)) through grant funding mechanisms such as EU's H2020 (Andersson, 2012). The goals of these initiatives are to decrease failure rates, expenses, and timelines for drug and evidence-based product and solution development. In parallel with these government-funded programs, the U.S. Food and Drug Administration's Critical Path Initiative (Woodcock and Woosley, 2008), the European Union's Innovative Medicine Initiative (Goldman, 2012), and the European Advanced Translational Research Infrastructure in Medicine (EATRIS — http://www.eatris.eu/) were initiated to foster public–private partnerships to enhance translation of basic biomedical research into patient- and consumer-end products and solutions. Not long ago, "translational" was an acronym for applied research or development (i.e. the "D" in "R&D"), an anathema to many investigators conducting basic research. However, recent scientific, technological and societal developments are now causing a re-assessment of the negative connotation of "applied" and "development" and the – in our view misleading – idea that "translational" and "basic" are either/or activities: translational research simply seeks to combine the best science with applications in real time for

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citizens and societies. Rather than esoterically distinguishing "basic" from "applied" science, we propose here to challenge and leverage basic science for its *relevance* to human health and societal benefits. This more recent approach and emerging scientific attitude root in four developments that we will outline hereunder: (1) evidence-based solutions; (2) "big data"; (3) consumer/patient empowerment; and (4) system thinking.

2. Development 1: The increasing need for evidenced-based solutions

The increasing prevalence of complex, age-related chronic diseases in developing and emerging economies is intensifying scientific, ethical and economic calls to improve the healthcare system (Callahan, 2013) and act on related health disparities (Dankwa-Mullan et al., 2010). Governments, companies, and philanthropic organizations recognize these realities and are now challenging investigators in "basic" research fields to translate their findings to actionable knowledge or products (Hobin et al., 2012). The burden is intense for the genomics field, which (over)promised rapid solutions to disease from leveraging data from the Human Genome (Consortium, 2001; Venter et al., 2001), HapMap (International HapMap Consortium, 2003), and related projects on human genetic diversity (Li et al., 2008; Siva, 2008).

3. Development 2: High-throughput laboratory and clinical data generation

The second development reinforcing the concept that basic research can be translatable is the ongoing evolution in the ability to quantify physiologies and genetic makeups of large numbers of study participants and patients using omics-based and imaging technologies. "Omics" analysis is meant to suggest a comprehensive analysis of molecules (i.e., genes/transcripts/proteins/lipids/metabolites) but in reality means as many molecules as the technology allows, with ranges of ~10s of chemically similar molecules (e.g., water-soluble organic micronutrients) to millions and soon billions of DNA bases.

In many cases, omic analysis is done with untargeted methods in a high-throughput screen (e.g. NMR-based metabonomics, or MS-based proteomics), which is then followed by more targeted and hence more sensitive methods focusing on a subset of molecules. Targeted quantification requires specific method development, in contrast to the generic screening methods. Such hypothesis-limited (Editorial, 1999) approaches differ from assessing a specific research question by means of measuring selected molecular readouts but promise to provide more comprehensive understanding of biological processes thanks to conceptually unbiased analysis (Kaput and Morine, 2012). These omics sciences have evolved over the last few decades and are prime examples of how technology has transformed and driven biomedical and other areas of biology research.

4. Development 3: Self-quantification and consumer empowerment

Knowledge-bases and clinical/diagnostic translations are outcomes of omics research, which essentially provide the dictionaries of components of human life. In almost all cases however, omics databases provide information about population averages or ranges for a molecule in a biofluid (e.g., Human Metabolome Database — http://www.hmdb.ca). In many such cases, these ranges are specific to the tested population since not all (or even many) ancestral genetic makeups have been sampled. Public health recommendations and clinical care are often based on the information captured in these databases but the information has to be individually adapted to the patient/consumer/person. Omics data obtained from analyzing one person has demonstrated the long-known facts of biochemical and genetic individuality (Williams, 1956).

The growing self-quantification movement and several citizen science research projects are disrupting the population average database model since individuals are now sharing n-of-1 data, including genomic information. This open genome and personal data access movement started with the Personal Genome Project at Harvard, which sequenced and allowed access to the genomes of 10 individuals (Church, 2005; Lunshof et al., 2010). An individual can obtain his/her genetic data from commercial companies (such as 23andme, FamilyTreeDNA). While the U.S. FDA has restricted these and other companies from providing associations to trait, phenotype, or disease (Green and Farahany, 2014), no restrictions were placed on the right of individuals to own their personal data (Angrist, 2014). Hence, individuals can and do share their data. OpenSNP (https://opensnp.org/) has about 2000 participants (accessed 18 April 2014) who have uploaded their genetic variation data, phenotypes, and traits with an option to allow their data to be downloaded by others for computational analysis. Associating individual genetic variants with complex phenotypes is less than robust (Ransohoff and Khoury, 2010) mitigating present-day concerns about the potential for discriminatory use of genomic data, However, ongoing research increasingly associates patterns of gene variants with susceptibilities to diseases and traits and privacy concerns are likely justified.

Access to individual genomic data holds great promise for making these associations. However, among the limiting factors for analyzing genetic data and outcomes is the lack of reliable and standardized dietary and lifestyle data, plus the missing access to personal omics data. A person's "molecular" phenotype is defined not only by classical measures such as body weight, blood pressure and clinical blood chemistry parameters, but also by their changing metabolites, transcripts, and proteins. Web-enabled research tools that capture, manage, store, and retrieve these personal molecular phenotype and lifestyle data are unavailable to the research community (Stumbo et al., 2010). NuGO, the former EU framework six-funded Nutrigenomics Organization and now scientific association (http://www.nugo.org), has launched the nutrition researcher cohort (NRC — http://www.nugo.org/nrc and (van Ommen, 2013)), an initiative to develop an open access cohort where each individual provides and owns her/his own health data that can be analyzed by the individual (e.g., (Chen et al., 2012)). However, the true strength of NRC will come from aggregating individual data with data from other members of the cohort (Monteiro et al., 2014; Nikles et al., 2011) to develop more in depth understanding of health phenotypes.

The smartphone revolution is being used by NRC and other initiatives since at least 500 apps (from http://quantifiedself.com/guide/ — 17 April 2014) exist to monitor all aspects of life including dietary intakes, sleep, moods, activity and physiological measures such as heart rate variability (Flatt and Esco, 2013), stress, blood glucose, or cholesterol levels (Oncescu et al., 2014). Healthcare (Boulos et al., 2011) and research activities may be transformed by the self-quantification movement if the diet and lifestyle data captured by apps and devices is of high quality and accuracy (Young et al., 2014). Data harmonization (Lynn et al., 2010; van Ommen et al., 2010) will also be essential for enabling system approaches to analysis of high dimensional data.

5. Development 4: System thinking and analysis

Modern biomedical research relies on very detailed mapping of biochemical reactions and interactions (e.g., http://web.expasy.org/cgi-bin/pathways/show_thumbnails.pl) that were generated largely from reductionist methods that examined each reaction either in isolation from other reactions or in limited biochemical contexts. While time-tested experimental methods continue to generate ever-finer details of these processes, the simple visual figures of biochemical transformations can give "the illusion of explanatory depth" (Rozenblit and Keil, 2002). Despite their utility for mechanistic research, biological outcomes can usually not be predicted from this knowledge base. Metabolism and its regulation form a complex interacting set of processes that change over time and in different environments.

System thinking and computational methods are now being increasingly used to help analyze and visualize biological systems such as

endocrine, circulatory, digestive, nervous, and immune functions as well as response to vaccines (Afacan et al., 2012; MacLellan et al., 2012; Poland et al., 2013; Slikker et al., 2007; van Ommen et al., 2008; Zhao et al., 2012). Modern system concepts (e.g., Hood et al., 2004) call for (i) high-throughput, quantitative measures of the genome, transcriptome, proteome, metabolome, and/or cytome levels; (ii) over time in homeostatic and challenged states, allowing metabolic flux analyses; (iii) integration and (meta-) analyses of data with computational network biology methods; and (iv) modeling to unravel mechanistic relationships of the biological processes.

Many of these system biology definitions and experimental approaches, however, miss the crucial inclusion of measuring environmental factors such as diet, psycho-social factors, physical activity, and other lifestyle factors, each of which may influence expression of genes, levels of proteins and metabolites (Kussmann et al., 2013). The human body is not a closed system as demonstrated by changes in blood concentrations of one-carbon metabolites and cofactors as a consequence of seasonal differences in nutrient availability (Dominguez-Salas et al., 2013).

Network-based methods describing health, subsystems of physiological processes, and pathological states (Mayer et al., 2013; Morine and Priami, 2013) provide the foundation for developing these systems-based models based on analysis of high-quality, high-dimensional genomic, proteomic, and/or metabolomic data with appropriate filtering from prospective and intervention studies. The conceptual pipeline (from (Kaput et al., 2014)) includes:

- Computational definition of system networks and sub-networks associated with health and pathologies and the underlying pathways, functional attributes, and mechanisms.
- Definition of biomarkers as hubs and bottlenecks connecting to different network elements of importance in signal transduction.
- Network simulations and flux analyses to unravel the dynamics and elasticity of physiological and pathological states and the impact of interventions.
- Simulations integrating molecular interactions and correlations.
- Computational predictions and actionable knowledge.

This pipeline can be operationalized using models of cellular responses, organs, systems, or conditions for designing and testing intervention or clinical studies. The initial (tissue-specific) framework, describing in molecular detail the processes of transport, metabolism and signaling in steady state, as well as during challenges with altered diet, physical activity, fasting, and sleeping may be developed from model organisms (van Ommen et al., 2009). However, and importantly for translational human genomics, system thinking and approaches can also be applied directly to humans in clinical settings with the additional concept that determining responses to diet, drugs, treatments, and vaccines based on genetic makeup and molecular phenotyping will be an iterative process (Kaput, 2008; Zazzu et al., 2013).

6. Perspectives

Model systems continue to play an important role for understanding disease and health processes since the types of experiments, control or knowledge of genetic variation, ability to regulate environmental variables, and accessibility to a range of tissues are greater than in human studies. However, the best model for developing an understanding of health and disease is the human. The paradigm shift (Kuhn, 1962) necessary in translational human health research is the recognition of the necessity to capture the complexity and dynamics of biological processes using omics in response to changing environmental exposures rather than trying to reduce this complexity to artificial levels that may be less meaningful for a real-life situation.

Translational genomics should therefore investigate how genomic and epigenomic individuality predisposes to health and disease and how an individual's genome expresses itself at different omic levels (proteomics, metabonomics, lipidomics) in response to environment, including e.g. nutrition and physical activity. This more comprehensive strategy requires extensive molecular phenotyping of humans which includes analysis of environmental, genomic, microbiological and epidemiological factors (Kaput and Morine, 2012; Kaput et al., 2014; Kussmann et al., 2013) and expansion of computational methods for data analysis:

1. A system approach to human health implies rethinking in vitro and in vivo models with regard to their translatability into human phenotypes: natural human cell models and panels of rodent strains should complement cancer cell lines and single rodent strains (Inselman et al., 2011).
2. Classical case/control designs of human clinical/nutritional intervention studies should be complemented by crossover, longitudinal studies, in which every subject is its own case and control (Kaput and Morine, 2012).
3. Human clinical study subjects should not only be assessed at homeostasis, e.g. fasting when the metabolic system is “at rest”, but also during a challenge to and restoration of homeostasis. Such safe challenges can be nutritional, physical, or cognitive in nature (van Ommen et al., 2009).
4. Classical genomic studies have been technology-driven rather than technology-rooted: the incentive to measure omic profiles of human subjects in clinical studies has often stemmed from recent developments and availability of genetic, epigenetic and omic platforms (Kussmann and Van Bladeren, 2011). This needs to be complemented by more comprehensive systems biology-based investigations deploying a multitude of omic platforms in an integrated fashion.
5. While comprehensive and quantitative omics are rapidly progressing in terms of data generation, quantitative capture and monitoring of the human environment, including diet, lifestyle, and socio-economic status have lagged behind. This limitation is now being addressed by more attractive and precise image-based consumer/research interfaces.
6. The bottleneck in knowledge generation has moved from the acquisition to processing, visualization and interpretation of the data. This requires innovative tools and methods including new ways of statistical treatment and biological network analysis.

In addition to capturing population-representative profiles, the era of personal (gen)omics is now emerging. Ultimately, the omics sciences form the analytical basis for an integrated, systematic and quantitative understanding of how a living system functions, be it an organelle, cell, organ, whole organism or even an entire ecosystem. This capability of simulating (“modeling”) a living system's behavior and predicting its responses towards external stimuli is the art of systems biology, which roots in a data-driven omics information culture. Translational research, and in particular translational genomics research expands pure fundamental science to augment the understanding of the physiological response of an individual to changing environments. This knowledge can form the basis to generate new solutions that can be applied in real time to assess, mitigate, improve, or delay disease symptoms and to maintain health.

Conflict of interest

The authors are employed by the Nestle Institute of Health Sciences.

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