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Translation of Genomics Research at the Bedside: the promise and the challenge

Damien Chaussabel

Baylor Institute for Immunology Research and Baylor Research Institute, Dallas TX

Much has already been written about the global perspective systems-scale studies have brought to the biomedical research field. It is this high vantage point that Kodama et al have chosen to identify candidate genes that may be involved in the pathogenesis of type 1 diabetes (T1D). The publication of this work gives us the opportunity to ponder the pathways leading to the translation of genomics research into therapies and diagnostics that will benefit patient at the bedside.

Indeed, we have not yet found a clear path for the translation of genomics research into medical advances. The field of genomics has been fueled by remarkable technological accomplishments, with the first widely publicized step being the sequencing of the human genome, followed next by the introduction of gene expression microarrays and more recently single nucleotide polymorphism (SNP) genotyping chips. These technologies have now reached a level of maturity sufficient to produce high quality data at low cost. In fact, the next technological revolution is already upon us with the recent introduction of high-throughput sequencers that will permit to accomplish all of the above better, faster and, now that the race for the \$1000 genome is in on, eventually at a much lower cost. Although it is hard resisting the impulse of associating this new wave of technological breakthrough to commensurate medical advances we should know by now that it might not necessarily happen, or at least not immediately. Indeed, while genome-wide investigations (gene expression, SNP studies) are in fact already having an impact on the lives of patients these initial advances have fallen far short of initial expectations. Part of it may be due to the fact that these expectations have been too high to start with, but on the other end the changes brought by these technologies at the bench have been nothing short of a quantum leap; so what about the bedside?

Significant challenges have gotten in the way and as of yet have not been fully addressed. Indeed we have learned over the past few years that systems scale molecular profiling comes with a price.

First of all, we must learn to cope with the scale of the data being produced. Whereas generating data has become downright straightforward the real difficulty lies in the identification of biomarkers or therapeutic targets from a vast pool of potential candidates. Indeed, there are many decisions to make in the face of many choices: which controls to use, how many replicates, which platform, which normalization strategy, which statistical cutoff or multiple testing correction strategy, etc... At the end of the day instead of obtaining a definite result, scientists have to deal with one version of the results that would have been quite different if a few more or less judicious choices had been made upstream in the analysis. Furthermore,

multiple comparisons carried out on such a scale inevitably generate false positive results (i.e. noise). Such noise can in turn affect the stability of biomarker signatures, and it may also lead to spurious biological interpretations. As a consequence it is difficult to be absolutely confident that the few transcripts that have been selected through this process are the “right” ones or the best possible ones. This lack of certainty can be unsettling and for many scientists proves often difficult to accept. Systems scale profiling also poses peculiar challenges when it comes to interpreting results. Indeed it is impossible for investigators to grasp the information generated by genome-wide screens as it comes out of the instrument. It is necessary to establish connections between elements, reduce dimension and devise visualization strategies that will aid the interpretation of the data (1,2).

Beyond having to deal with the scale of the data it is also important to be able to identify and control sources of variability. In most studies variability will come in two flavors: technical and biological. Technical variability can arise at multiple levels, from sample collection (e.g. sampling and isolation procedures), processing (e.g. RNA extraction, labeling), and data acquisition (e.g. washing, staining, chip lot number). Controlling technical variability is particularly critical when working with gene expression microarrays. The signals being generated are semi-quantitative also the results of the analysis will rely on the comparisons that are made among samples or groups of samples. Therefore, it is essential to control technical source of variability in order to avoid confounding the analysis. The solution consist in running complete sets of samples in large batches including all necessary controls, develop standard procedures and automate as many as the sample processing steps as possible. Biological variability also needs to be taken into account, in particular in patient-based studies where inter-individual variability may be attributed to differences in genetic background, environmental influences and disease heterogeneity (different forms of the disease, different stages, co-morbidities, treatments, etc.). The careful clinical evaluation and selection of patients is therefore often going to dictate the success or failure of a study. In conclusion, it is important in any given systems scale study or experiment to grasp the nature and extent of variability that may affect the interpretation of the results.

Komada et al, have looked past these challenges at the opportunities offered by genome-wide screening technologies for the identification of novel biomarkers and therapeutic targets. This group has endeavored to unravel mechanisms of pathogenesis and discover clinically-relevant markers in T1D using gene expression microarrays. The experiment they have designed yielded a comprehensive view of the molecular perturbations occurring during the development of the disease in the lymph nodes, spleen and peripheral blood of NOD mice. Combining this data with the knowledge of T1D susceptibility region yielded potential candidate genes that may prove critical in the future development of therapeutic modalities. From a broader perspective, this work is also remarkable because it reveals that the pathogenic process can alone drive transcriptional perturbations which are measurable over time and in different tissues.

While Komada et al. chose to study an animal model of a disease, genomic analysis tools have in recent years also been increasingly employed in patient-based studies. It is therefore interesting to contrast these two approaches with respect to the set of challenges posed by genomics research that we have enunciated above.

Genomic transcriptional studies carried out in an animal model or a patient population are subjected to the constraints inherent to systems scale analyses but differ fundamentally on two aspects. First, working with model organisms affords exquisite control over biological variables. This fact is perfectly illustrated by Komada et al. who were able to design a very elegant experiment, using in their study the NOD.B10 mice that is in all respect are similar to the NOD strain but for the fact that they cannot present the disease provoking epitope and serve therefore as the “non-disease expressing twin”. It is therefore possible to employ age- and sex-

matched genetic clones that are kept in a similar environment. This situation is a far cry from patient studies, where differences in genetic background, lifestyle, co-morbidities or treatment all contribute to augment extraneous biological variability, hence the need for carrying out human studies on a much larger scale and appeal of pediatric settings where a number of these variables are often minimized. The second fundamental aspect distinguishing animal model and patient based studies is obviously the relevance of the findings with regards to human health. It means that, despite the inherent limitations associated with working with human subjects, results of patient-based study may quickly find a direct application at the bedside. Also patient-based work has led over the past few years to the discovery of novel treatment modalities and diagnostic biomarkers (1,3–9). Indeed, the recent availability of high-resolution molecular profiling tools offers an unprecedented opportunity to study human diseases “in nature”, thus encouraging the bedside to the bench, back to the bedside model.

What is common to animal model- and patient-based studies is the fact that at the end of an elaborate selection process candidates will be identified that will require further investigation. While such studies do not yield definitive scientific conclusion they are of importance because they support the generation of novel hypotheses. Therefore, in order for this research to come to fruition it is essential that it integrates a rationalized downstream discovery process. There is obviously work to be done in this area but an in depth discussion of current shortcomings is beyond the scope of this editorial.

In conclusion, genomics research can be a powerful driver for discoveries that will have a dramatic impact on health care. In order to realize this potential it is necessary to become more efficient at leveraging systems scale results produced at increasingly higher rates. This means implementing ad hoc mining and visualization strategies, but also improving means to integrate data from multiple sources and developing downstream discovery pipelines.

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