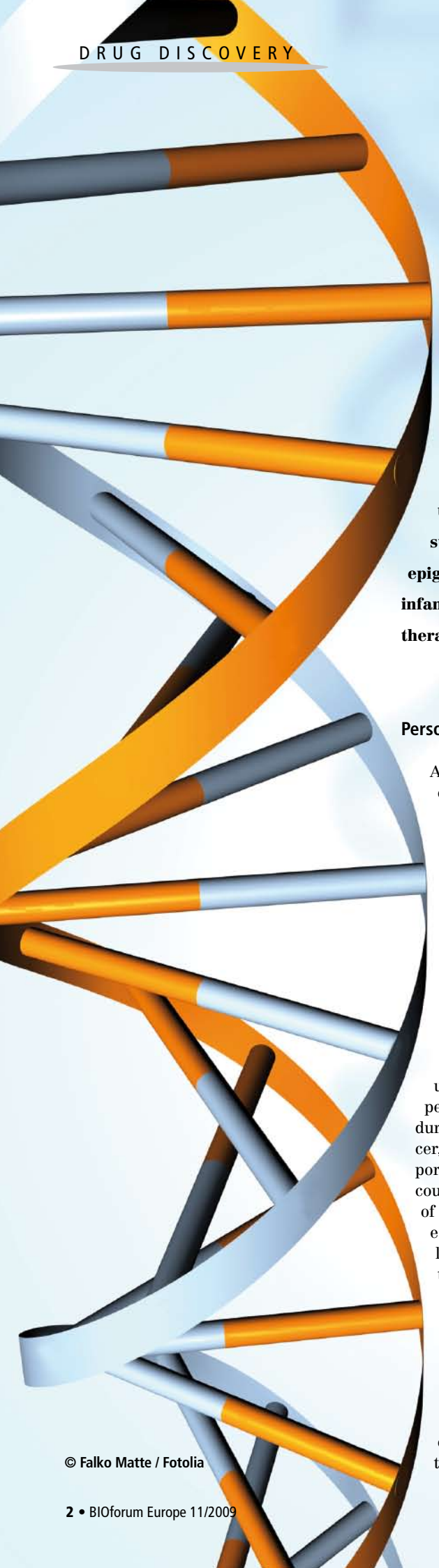

Genomics, Epigenomics and Personalized Medicine

A Bright Future for Drug Development?

The sequencing of the human genome marked the beginning of two new fields: personalized genomics and epigenomics. Some companies have already launched personalized genetic tests and whole genome sequencing to predict diseases. Epigenomics has also emerged in the post-genomic era with the objective of cataloguing all modifications in the DNA that have the potential to change the expression of genes. Epigenetics refers to the study of such changes and some drugs have already been launched based in epigenetic mechanisms. This is just the beginning for two fields that are in their infancy and it is clear that new medicines that could revolutionize personalized therapies are on the way.

Personal Genomics Comes of Age

An array of different services has recently emerged based on whole-genome association studies and whole genome sequencing. This has been possible mainly due to the emergence of new DNA sequencing technologies. These new technologies, and others that are in development, will enable the sequencing of a human genome at a previously unimagined throughput and at a very low cost. Using these new methodologies, companies can already offer to sequence an individual's genome and give a follow up on the possible diseases that a person is more susceptible to develop during his or her lifetime such as cancer, diabetis, Alzheimer's, etc. One important factor that is not taken into account in these genetic tests is the power of the environment in multigenic diseases. Depending on an individual's lifestyle and exposures during life, the probabilities of developing a disease could change. This can be explained mainly because of the interactions between the environment and the genome. Growing evidence suggests that this is an important factor and is related to a field called epigenetics. Epigenetics is the study of modifications in specific loci in the genome that do not change the sequence of DNA but can change gene expression by different mechanisms and the epigenome is defined as the combination of all these changes. While we cannot deny the importance of environmental influence on the genome, we also cannot deny that personalized genomics can help individuals to take decisions and change their lifes depending on the results they get back from these predictive tests [1]. Personalized genomics will also help in the understanding of human variations and their impact in common diseases facilitating the development of more specific drugs.

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Epigenomics and the Post-Genomic Era

The main objective of epigenomics, which has marked the beginning of the

post-genomic era, is to catalog all modifications occurring in a genome that does not change the sequence of the bases in the DNA. As discussed above, epigenetics represents the study of these modifications in specific loci in the genome. The main epigenetic modifications that can occur in a human genome are: a) the binding of different proteins in the DNA molecule such as histones, that change its conformation; b) the addition of different chemical groups in the DNA such as methyl (CH3) and; c) microRNAs (miRNAs) and other non-coding RNAs (ncRNAs) that can regulate gene expression by different mechanisms (for more details on epigenetic mechanisms see reference 2). DNA methylation or the addition of methyl groups in the DNA, has been extensively studied and changes in the normal pattern of methylation are associated to diseases such as cancer. Our studies have already shown that the gain of DNA methylation in the promoter region of important genes [3, 4] and loss of DNA methylation in repetitive sequences [5] are associated to the tumorigenesis process. Additionally, our group is also interested in expression changes of genes, such as ncRNAs, in diseases. ncRNAs are a growing class of genes that are implicated in different epigenetic mechanisms and do not code for proteins [6, 7]. miRNAs are very small ncRNAs that have a big impact in eukaryotic cells; they can regulate hundreds to thousands of protein-coding genes [6, 7]. miRNA expression changes have important implications in gene networks and pathways by mechanisms that are still being deciphered by scientists. Deregulated expression of miRNAs has also been shown as an important factor in the initiation and progression of diseases reinforcing their impact in gene regulation [8].

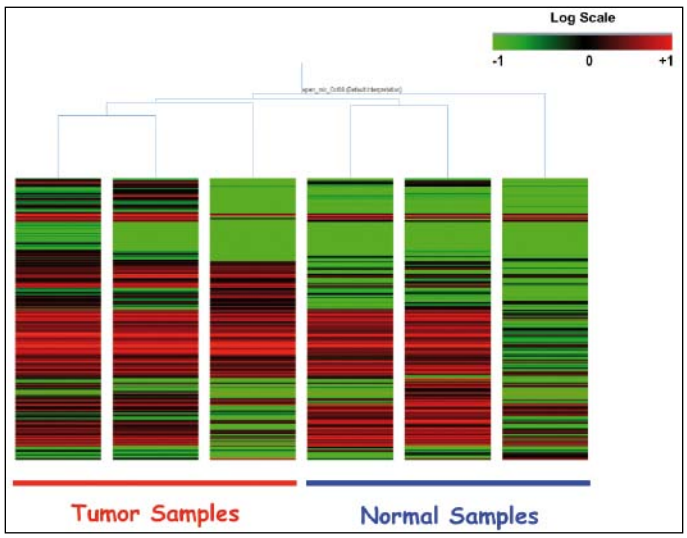

Fig.1: Example of a miRNA expression profile in cancer. Representative example miRNA expression analyses of three tumor samples compared to three normal samples. The figure depicts "heat maps" for ~400 miRNAs. Each line represents the expression data for a miRNA. Green colors indicate low expression and red colors indicate high expression of specific miRNAs in each sample. These differences could be important for clinical decisions and for the development of more specific drugs. Credits for this figure: Dr Min Wang.

Therapeutic Implications

Epigenetic changes are implicated in a variety of diseases as discussed above mainly because these mechanisms are the basis for the normal development of an organism. Diseases such as cancer and neurological diseases such as Angelman Syndrome, Prader-Willi Syndrome, Rett Syndrome, and others are mainly caused by defects in epigenetics. Importantly, in contrast to genetic mutations, most epigenetic modifications can be reversible and preventable. Some drugs have already been developed based on epigenetics and entered the market such as histone deacetylase (HDACs) inhibitors, DNA methyl transferase (DNMTs) inhibitors, and also drugs targeting histone methyltransferases (HMTs), polycomb proteins, etc. Some of these drugs have already been approved by the FDA for some types of cancer and others are in clinical trials but they are not very specific and have side effects. Companies have been trying to improve their mechanisms of action to overcome the side effects and also combine these drugs with others. The main goal of the majority of the studies involving genomics and epigenomics is to identify defects in networks of genes and develop more specific drugs for multigenic diseases. This goal is very challenging since hundreds of protein-coding genes can participate in a single deficient network in a disease. Since miRNAs have the ability to regulate several protein-coding genes in a "one-hit multiple target" fashion, they have recently become a subject of interest in academia and in the private sector [8]. Companies have been developing drugs to inhibit and/or to over-express these master regulators using different strategies. Moreover, expression profiles generated with miRNAs in cancer have shown that they are more reliable in predicting the outcome and in providing a better diagnosis for diseases than genes that code for proteins (see fig.1 for miRNA expression profiles in tumors). In addition, miRNA variations have also been implicated in mechanisms of drug metabolism and activation showing that these genes might be important in drug response as well [9]. Thus, the identification and cataloging of these variations will be of importance for a better understanding of diseases and for the development of more specific drugs. Personalized medicine will need to include miRNAs as very important markers for clinical decisions. Importantly, other less known components of the epigenome such as long or large RNAs, have also been identified [10]. Several lines of evidence indicate that they could be used as very specific targets for drug development and as biomarkers in different diseases, especially cancer [10].

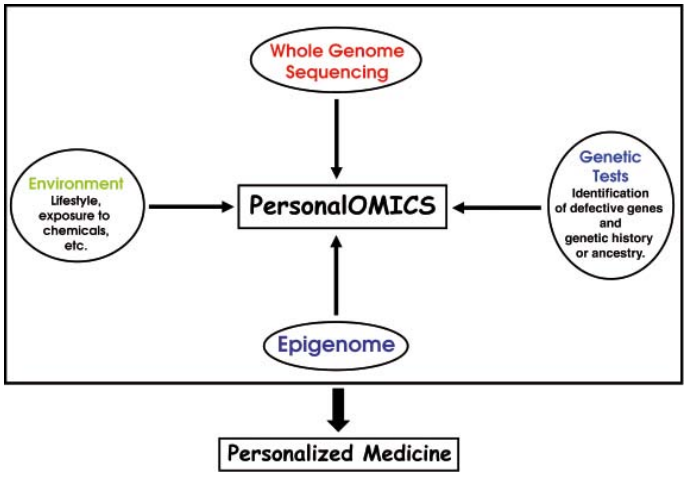

Fig. 2: Schematic representation of different components of the emerging field of personalized medicine. In this model, complete sequencing of an individual's genome, predictive genetic tests using genome association studies, the epigenome and the environment combined can give rise to a new concept called PersonalOMICS.

Conclusions

Great challenges, including the use of more specific drugs with fewer side effects and less toxicity, lie ahead for personalized medicine to be applied to clinical medicine. However, recent breakthroughs and new technologies have been developed and launched. These technologies, together with the identification of important components of the epigenome, are improving our pipelines for drug discovery and the development of more specific medicines. Whole genome studies and sequencing will allow the identification of groups of defective genes implicated in multigenic diseases and also identify specific genes associated to monogenic diseases that are not completely understood. Moreover, the emergence of epigenomics with miRNAs and other ncRNAs as major players will be important for the identification of defects in entire networks involved in diseases facilitating the development of better drugs. In the future, we can expect a revolution in medicine with completely different approaches for disease treatment (for a complete overview of all components that will have implications in personalized medicine see fig. 2). Personalized medicine may become a new OMICS – PersonalOMICS – that will represent the complete package of information about an individual's genome, epigenome and also a catalog of their own defective genes.

References are available from the author.

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