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Review Article

Advances in individualized and regenerative medicine

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ABSTRACT

Molecular and cell biology have resulted in major advances in our understanding of disease pathogenesis as well as in novel strategies for the diagnosis, therapy and prevention of human diseases. Based on modern molecular, genetic and biochemical methodologies it is on the one hand possible to identify for example disease-related point mutations and single nucleotide polymorphisms. On the other hand, using high throughput array and other technologies, it is for example possible to simultaneously analyze thousands of genes or gene products (RNA and proteins), resulting in an individual gene or gene expression profile ('signature'). Such data increasingly allow to define the individual disposition for a given disease and to predict disease prognosis as well as the efficacy of therapeutic strategies in the individual patient ('individualized medicine'). At the same time, the basic discoveries in cell biology, including embryonic and adult stem cells, induced pluripotent stem cells, genetically modified cells and others, have moved regenerative medicine into the center of biomedical research worldwide with a major translational impact on tissue engineering as well as transplantation medicine. All these aspects have greatly contributed to the recent advances in regenerative medicine and the development novel concepts for the treatment of many human diseases, including liver diseases.

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1. Introduction

The basic aspects of molecular and cell biology are not only integral part of biomedical research but are increasingly also translated into patient care. The genetic material of all living organisms is made up of DNA that in its entirety makes up the individual's genome. Three major global research efforts have been launched and in part completed during the last 2 decades:

(1) The international human genome organization (HUGO) project established the complete sequence of the human genome more than ten years ago [1,2]. In order to utilize the sequence information from the HUGO project for research as well as for clinical applications and to define the function(s) of newly

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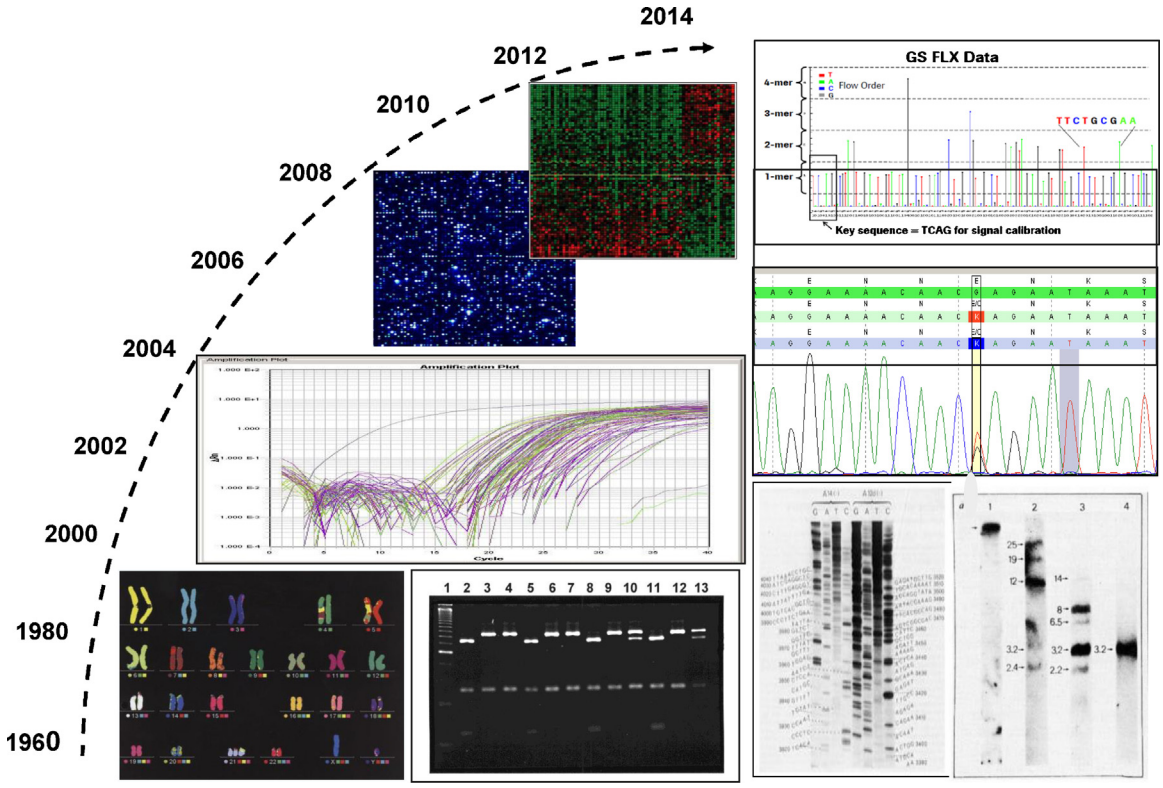

Fig. 1. Molecular and cell biology analyses: 1960s–date.

identified genes, collectively termed 'functional genomics', strategies were developed to globally analyze genomic DNA sequences as well as their cell-, tissue- or organ-specific expression profile. Using chips, so-called 'microarrays' (Fig. 1), thousands or ten thousands of single-stranded DNA species, reverse transcribed RNA (cDNA) or oligonucleotides of known sequence provide a global gene (genomics), gene expression (transcriptomics, proteomics) or metabolite (metabolomics) profile ('signature') that is characteristic for a specific human disease.

(2) In 2005, the international haplotype map (HapMap) project was initiated to identify, based on genome-wide association studies (GWAS) in 4 ethnically different populations, single nucleotide polymorphisms (SNPs) and their association with specific human diseases and individual phenotypic characteristics, respectively [3–6]. Through GWAS more than 200 gene loci have been identified that are associated with individual phenotypic traits, such as hair or eye color, height, body mass index and others or with the individual disposition to develop a specific disease (Fig. 2) [5,6]. Examples are the individual risk to develop coronary heart disease [7,8], restless legs syndrome [9], sporadic amyotrophic lateral sclerosis [10] or multiple sclerosis [11] and many others [12]. Furthermore, a polymorphism in the apolipoprotein C3 gene has recently been found to be associated with non-alcoholic steatohepatitis (NASH) and insulin resistance [13]. For hepatocellular carcinoma (HCC), a G/G polymorphism in the epidermal growth factor (EGF) gene was found to be associated with a 4-fold increased HCC risk [14]. Also with respect to the individual breast cancer risk, GWAS identified several gene loci [5]. GWAS, therefore, allow an increasingly better understanding of disease pathogenesis and assessment of the individual risk to develop a specific disease. Clinically, this may eventually translate into improvements in disease prevention, early diagnosis and therapy. It should be cautioned, however, that the contribution of a defined SNP to the risk assessment for a given disease must, for each disease entity, be carefully weighed against established clinical parameters. In this context, a recently published study found an only marginal contribution of genetic data to the assessment of the individual breast cancer risk compared to the clinically established Gail model [15]. Taken together, despite the tremendous potential of GWAS, the clinical relevance of SNPs for the prediction the individual traits or disease risks needs to be carefully evaluated [16,17].

(3) A third global consortium, termed human microbiome project (HMP), was established in 2007. The HMP aims at the documentation of all sequences of the human microbiome, including the mouth, throat and airways, stomach and intestine, urogenital and skin microbiomes, respectively, and their association with human health and diseases [18–21]. Recent clinical examples are a causal relationship between the gut microbiome and kwashiorkor [22], obesity-associated HCC [23] and the metabolic syndrome [24], respectively. The emerging data suggest that the detailed characterization of the human microbiome composition, function and variation across different body sites will reveal important commensal host–microbe as well as microbe–microbe interactions that may play a role in human health and disease with diagnostic as well as therapeutic implications [25]. In the following, the principle of transgene and nuclear transfer technologies as well as the current state of individualized and regenerative medicine are reviewed.

2. Review

2.1. Transgene and nuclear transfer technologies

Fertilization of mammalian eggs is followed by successive cell divisions and stages of the embryo, incl. blastomere,