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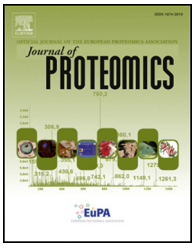

Review

Individualized proteomics☆

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ABSTRACT

Human individuals differ from one another in almost all of their genes due to single nucleotide polymorphisms (SNPs). When the maternal and the paternal genomes become combined in a F1 individual, the two alleles of each gene represent arbitrary combinations. In consequence, individuals show high variability in protein expression. Furthermore, within a proteome, the proteins form networks of protein–protein interactions. These networks differ between individuals in robustness against genetic or/and environmental perturbation due to polymorphisms, which differ in type and composition between individuals, and modify the arrangement of proteins in the proteomic network. As a general conclusion, the robustness of a human individual against diseases may depend on the structure and expression of the protein–protein interaction network that varies in its functional efficiency between individuals due to "network-polymorphisms".
This article is part of a Special Issue entitled: 20 years of Proteomics.

Contents

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1. Variation in the genome-wide DNA sequences between individuals

All humans have the same genes but between genes differences (alleles) frequently occur. Most frequently these are single nucleotide polymorphisms (SNP). In the framework of the "1000 Genomes Project", 3.70 Mill. SNPs were found on average per individual [1]. In a human population, most of the SNPs of a distinct gene occur with a frequency >5% [1]. However, when we calculated from the published data [1] how many SNPs two arbitrarily selected persons may have in common, we found that this number is as low as 0.04% (data of 85 individuals tested). This means that genetically – including coding as well as noncoding (regulatory) sequences – each human individual actually differs almost totally from one another.

The individualized composition of the genome became quite obvious in a recent publication [2,3]. Here the genome of a single human individual was sequenced and the two haploid genomes, that from the father and that from the mother, were compared. This allowed us to recognize homozygous and heterozygous loci. In one gene, several SNPs can occur, and under heterozygote conditions they differ in the cis–trans configuration. Consequently, the SNPs of the two allelic genes can occur in different combinations, and in this way create different haplotypes. Entire genomic regions could be separated into underlying haploid landscapes with an extension of up to ~6.3 Mb [2]. It has been shown that different haplotypes have different effects on the phenotype [2,4]. Therefore, even if two individuals have the same SNPs in the same gene, they may show different phenotypes due to the different haplotypes generated by these genes.

In the comparison of the maternal versus paternal genome of a human individual [2], almost all of the 17,861 autosomal protein-coding genes could be deciphered for each of the two homologous chromosomes. In this analysis, an adjacent region 5.8 Mb upstream and downstream of the genes was included. The results show that about 90% of the genes have two different molecular forms differing in at least two base positions. The proteins from two haplotypes can differ in expression and in extreme cases (20%) represent two different proteins. The ability of the genome to activate different haplotypic or diplotypic combinations of genes and regulatory elements was found to point to the high versatility of a diploid genome and indicates a strong individual component. The small proportion (13.7%) of genes that were invariable between the two homologous chromosomes showed overrepresentation of GO ontologies for development processes, which is in accordance with their conservation.

2. Genetic variability and robustness of the proteome of different individuals

As concluded from the above mentioned results published on sequencing the total human genome, individuals actually differ from one another in almost all of their genes; most frequently by single nucleotide polymorphisms. Accordingly, one can expect that also all the proteins differ genetically between individuals. Proteins, however, can differ in several respects: quantitatively depending on regulatory DNA sequences, structurally by changes in the amino acid sequences, frequently including changes in conformation, and in addition, by many post-translational modifications. Moreover, proteins become trans-variant by interaction with primarily variant (cis-variant) proteins. In total, the genetic variability of proteins may have consequences for the individual regulation of the entire highly complex network of protein–protein interaction.

The expression level of a protein depends on the regulation of the functional interactions of proteins of the pathway in which it is involved. In this process, up-regulation and down-regulation of a protein are balanced, i.e. kept in steady-state. Moreover, since proteins are connected in proteome-wide networks and sub-nets of protein interactions the whole proteomic system must be kept in balance (homeostasis) [5,23]. On the other hand, protein expression must be flexible enough to be able to compensate genetic and environmental perturbations. In this context it is interesting to consider the fact, outlined above, that the genome of each individual is specifically characterized genome-wide by its combined polymorphisms. Here the critical situation is that the two alleles of each gene, that from the mother and that from the father, always come together in the progeny arbitrarily. This should result in a rather "chaotic" composition of the protein expression levels of the cell. However, global regulatory mechanisms, acting at the protein level [6], adapt the proteins involved in the various functional pathways and sub-networks of protein–protein interactions in a way that leads to a balanced proteome. Indeed, it was found that proteins which are part of the same protein complex, or occur in the same biological process, vary synchronously [6], and interacting proteins are more likely to be encoded by genes with similar expression profiles than noninteracting proteins [7]. This shows that the expression levels of the various proteins became integrated into a common system of interaction. Therefore, one can expect that different arrangements in regulating protein expression and interaction take place in different individuals to reach a well-balanced proteome. But this must not necessarily lead to optimal conditions in each case. It has been distinguished between networks of "perfect" and "partial" homeostasis [8]. This suggests that the arbitrary combination of polymorphisms results in a proteomic network that differs from individual to individual in its robustness against perturbations. In one case the proteome is able to react against a disease by a high buffer capacity in protein expression and by offering alternative pathways in proteomic networking. In another individual, the proteomic network may be more static and not flexible enough to adapt to the altered conditions.

Robustness against perturbations has been considered as one of the fundamental characteristics of biological systems, and was defined as a property that allows a system to maintain its function even under internal (genetic) or external (environment) perturbations [9,10]. Robustness has been observed from the level of gene transcription to the level of systemic homeostasis [9,10]. According to a review published by Jarosz et al. [5], mechanisms contributing to phenotypic

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