Drug adverse reactions predictability: exploring the mechanisms underlying the unexplained interindividual differences in drug metabolism and transport

Results in Brief

Mechanisms of drug response variability

Adverse drug reactions (ADRs) often require hospital admissions, with increasing frequency especially in elderly patients. European scientists focused on the individual variability in drug response and metabolism in relation to ADRs.

FUNDAMENTAL RESEARCH

HEALTH

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Currently, only about 30 to 60 % of patients show proper response to treatment with such drugs as antidepressants, beta-blockers, statins or antipsychotics. It is established that epigenetic modifications play an important role in the regulation of human genes involved in absorption, distribution, metabolism and excretion (ADME) of drugs. In certain cases, epigenetic modifications can be monitored not only in the affected tissues but also in body fluids in the form of DNA elements originating from the tissues. Such circulating DNA elements represent a novel class of epigenetic biomarkers that could be critical for drug therapy individualisation and improvement.

The EU-funded DARMEC (Drug adverse reactions predictability: Exploring the mechanisms underlying the unexplained interindividual differences in drug metabolism and transport) project worked to understand the significance of individual variability in drug response using a 3D multi-cell in vitro model of the human liver. Researchers set out to create a list of epigenetically regulated ADME genes and to investigate the role of the modifications, establishing a stable model for chronic drug exposure.

Scientists have identified DNA hydroxymethylation as a functionally important epigenetic marker in the liver and developed technology allowing the base-pair discrimination between DNA methylation and hydroxymethylation. Additionally, they defined the combinations of genetic and DNA methylation variations that are specific to the liver, muscle and adipose tissue.

Important project achievements included establishment and characterisation of the liver and muscle organotypic cultures for long-term study of the drugs that affect both the transcriptome and the epigenome. This approach has allowed defining a list of genes subject to epigenetic regulation as potential biomarkers of drug response and targets for intervention against drug resistance. It also demonstrated, for the first time in the human liver, the dynamics in gene expression associated with global variations in DNA methylation and hydroxymethylation in a panel of genes important for drug metabolism.

Finally, the analysis of DNA methylation, hydroxymethylation and transcription in 130 human livers identified that individual hydroxymethylation levels vary significantly and that genomic distribution of hydroxymethylation is non-uniform along the chromosomes. Importantly, DARMEC results uncover a complete new potential approach for identifying the regulatory roles of this recently rediscovered DNA epigenetic modification.

Keywords

Adverse drug reactions, epigenetic modifications, circulating DNA elements, epigenetic biomarkers, DARMEC

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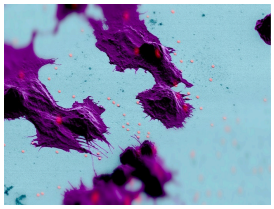

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