PREDICTIVE TOXICOGENOMICS FOR CANCER RISK ASSESSMENT

NAPOVEDNA TOKSIKOGENOMIKA IN OCENA TVEGANJA ZA NASTANEK RAKA

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Abstract *Every organism, and therefore also humans, is the product of its genes in combination with its environment. The activity of genes is strictly regulated and is continuously liable to changes. The response of an organism to changes in its environment, such as the exposure to a toxic substance, leads to altered gene expressions. Analysing modified gene expression profiles as a result of exposure to chemical substances, can therefore aid to determine the hazardous properties of those substances, such as on carcinogenic capacity. This toxicogenomics approach also provides the possibility to drastically reduce the traditional animal tests.*

Key words *risk assessment; cancer; toxicogenomics*

Izvleček *Vsak organizem, tudi človeški, je produkt delovanja lastnih genov v kombinaciji z dejavniki okolja. Aktivnost genov je strogo uravnavana in nenehno podvržena spremembam. Organizem se na spremembe v svojem okolju, na primer na izpostavljenost toksičnim snovem, odzove s spremembami v izražanju genov. Z analizo sprememb v izražanju genov, ki so posledica izpostavljenosti kemičnim snovem, lahko določamo škodljive učinke teh snovi, kot je npr. stopnja kancerogenosti. S takim toksikogenomskim pristopom lahko bistveno zmanjšamo uporabo tradicionalnih testov na živalih.*

Ključne besede *ocena tveganja; rak; toksikogenomika*

The central dogma in molecular biology is that DNA encodes for RNA (transcription), RNA encode for proteins (translation), and these proteins are the construction tools and engines in the cell by which all processes are regulated and carried out. Most proteins are enzymes which have a catalytic function in cell, whereby substances are converted – metabolised – into another substance. This may also imply that another protein is modified, for example because a phosphate group is coupled to it, as a result of which this protein becomes active or inactive.

Controlling the activity of genes, and with that of proteins such as enzymes and therefore also the metabolites which reside in cell, is very complex and takes place at several levels: 1) from within the cell itself, like for example the case at programmed cell death (apoptosis), 2) by other cells in the body, like for example in the immune system, where one immune cell may influence the functioning of another immune cell, and 3) influences from outside the body, like as a result of exposure to a toxic substance. A well-known example of the latter is dioxin, a carcinogenic substance which binds to a sensor in the cell and as a result of that, becomes a regulator of transcription and raises the activity of a many genes drastically, thereby eventually leading to the development of cancer.[1–3]

In the last decade, methods have become available, which enable to simultaneously analyse the activity of all genes, or the quantities of all proteins or of all cellular metabolites. For measuring the expression of all genes, DNA microarrays have been developed, which eventually results in genome-wide gene expression profiles. Changes in these gene expression profiles reflect modifications in the activities of all genes.[4, 5] For proteins and metabolites other methods have been developed, but these will not be discussed here.

Since exposure of humans and animals to chemical substances leads to changed gene activities in the body, analysing these modulations may therefore have very interesting applications for toxicology. Toxicology namely investigates whether chemical substances have hazardous impact on humans or animals, and importantly also, to retrieve the mechanisms of action. Establishing these so-called genomic risk profiles has a central role in toxicogenomics.[6–9]

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New drugs, chemicals or ingredients of cosmetic products can only be put on the market, if they have been demonstrated to be safe for humans or animals. This means that each new substance is extensively examined on possible hazardous properties. Although already a lot can be achieved by tests on cultured cells, animal tests are however still necessary. It is expected that investigating genomic risk profiles – thus toxicogenomics – drastically reduces the use of test animals, and thereby also provides wealthy information concerning the mechanisms of action of a substance.[10, 11]

Cancer can be caused by chemical substances. Carcinogenic potency is therefore an crucial toxic property, which must be examined to assess the safety of a substance. Two important mechanisms ensure that a substance is carcinogenic. First because the substance damages the DNA, which leads to mutations (change of the genetic code), and as a result of this, a disorganised control of the cell growth (e. g. too many cell divisions or too less apoptosis). Examples of this are many cytostatic anti-cancer drugs and also carcinogenic compounds which are present in cigarette smoke. Secondly, the carcinogenic substances do not damage DNA, but cause by means of other – indirect – mechanisms a stimulation of the cell division or a suppression of the apoptosis.[12] Dioxin is a well-known example of such a carcinogen.

Predicting toxic properties of a substance by assessing gene expression profiles, requires that first a large database is built for well-known classes of toxic substances (see Figure 1, with carcinogens as example). That database consists of gene expression profiles for many substances per class. For each class, a gene expression profile can be identified by means of mathematical models, by which that class can be distinguished from others. Next, by comparing the gene expression profile of a new substance with those of the different toxic classes, the best fit with a specific class can be determined. Thereby, it can be assessed whether a substance has a specific toxic property.[13–16]

At the Department of Health Risk Analysis and Toxicology and in (inter)national collaborations (the Netherlands Toxicogenomics Centre [www.toxicogenomics centre.nl] and the Carcinogenomics project of the European Union [www.carcinogenomics.org]) extensive Toxicogenomics studies are conducted. These particularly aim at developing alternative methods for animal tests based on generating genomic risk profiles by microarray technologies, for carcinogenicity, for immunotoxicity and for reprotoxicity.

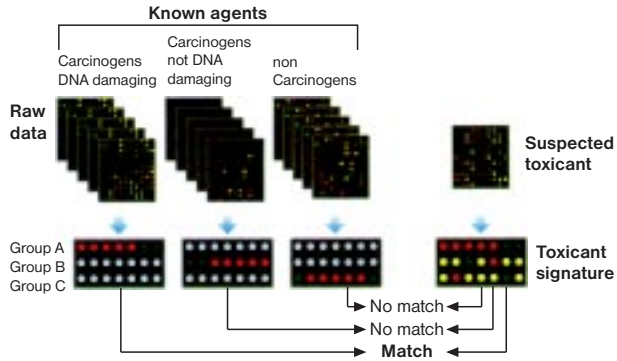

Figure 1. *Assessing the carcinogenic property of a chemical compound by means of gene expression profiling in exposed cells.*

Sl. 1. *Ugotavljanje kancerogenosti kemične snovi z ugotavljanjem sprememb v izražanju genov v izpostavljenih celicah.*

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