11
Cardiotoxicity of antitumor drugs

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Cardiotoxicity is an untoward effect of many antitumor drugs. Fluoropyrimidines, taxanes, and alkylating agents, may induce sporadic and dose-independent ischemia, arrhythmias, pericardial effusions; these are mediated by impurities of the pharmaceutical composition, unpredictable redox coupling of the drugs with myocardial electrophiles, hypersensitivity reactions. Doxorubicin and other anthracyclines induce a concentration-dependent and irreversible cardiomyopathy that culminates in a congestive heart failure. Anthracycline cardiotoxicity, often referred to as "type I", seems to develop in response to iron-mediated oxidative stress or metabolic perturbances mediated by secondary alcohol metabolites. These concepts have formed the basis to design iron chelators that prevent cardiotoxicity, or to develop anthracyclines that form fewer amounts of their secondary alcohol metabolites.

Over the last few years several target-oriented drugs were developed with the aim of suppressing tumor growth while not causing side effects at cardiac or extracardiac sites. Some of these drugs (like the antiHER-2/neu antibody Trastuzumab) exhibited a new type of cardiotoxicity that was referred to as "type II" and was considered to be "mild" in the light of criteria such as reversibility and little or no recurrence upon rechallenge. However, combining Trastuzumab with doxorubicin caused congestive heart failure at lower than expected cumulative doses of the anthracycline, as if the type II cardiotoxicity of Trastuzumab blocked survival pathways that mitigated the type I cardiotoxicity of doxorubicin. Many other targeted drugs might cause a type II cardiotoxicity. This justifies an intensified and long-term surveillance of the cardiac function of cancer patients treated with anthracyclines and targeted drugs.

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12
Chronic contamination with ^{137}Cesium in rat: Effect on cardiovascular system

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Following the accident at the Chernobyl Nuclear Power plant, a marked increase of various diseases was reported in the literature. Several impairments of the cardiovascular system have been observed in children and in liquidators but no experimental studies were undertaken by the chronic contamination of animals at post-accidental levels of cesium 137 (^{137}Cs).

Biochemical, physiological and molecular markers of the cardiovascular system were analysed in rats exposed through drinking water to ^{137}Cs at a dose of 500 Bq/kg (6500 Bq/l). Plasma concentration of CK and CK-MB, biochemical markers of cardiac damage, were higher (>52%, $p < 0.05$) in contaminated rats whereas no histological alteration of the heart appeared. Nevertheless, small modifications of heart gene expression were observed in the atria. Angiotensin converting enzyme (ACE), the rate-limiting enzyme of the renin-angiotensin system, and brain natriurectic peptide (BNP), involved in physiological regulation of blood pressure, were significantly increased ($p < 0.05$). ECG and blood pressure measurement were then undertaken to analyse if there were any physiological consequences. No arrhythmia was observed except ST- and RT-segment depression (−9% and −11%, respectively, $p < 0.05$) in rats exposed to ^{137}Cs. Furthermore, mean arterial blood pressure decreased (−10%, $p < 0.05$) in ^{137}Cs-exposed rats along with a disappearance of the blood pressure circadian rhythm.

Overall, chronic contamination with a post-accidental dose of ^{137}Cs during 3 months did not result in pathological disorder, but the impairments of the cardiovascular system observed could evolve to more significant alteration in sensitive animals or after a longer contamination.

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13
Time dependent activation of transcription factors in freshly isolated cardiomyocytes: Adrenaline and reactive oxygen species incubation

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The sustained elevation of plasma and interstitial catecholamine levels, namely adrenaline (ADR), in several pathologic conditions raises many questions in the cellular toxicity that those compounds can undertake. Additionally, when an ischemic/reperfusion feature is present, a burst of reactive species of oxygen (ROS) occurs. In the present study, we investigated the role of ROS production on the activation of transcription factors in freshly isolated adult rat cardiomyocytes exposed to ADR. Furthermore, the cardiomyocytes were also exposed to ADR with a system capable of generating ROS [xanthine and xanthine oxidase (X/XO)]. ROS production was measured with the fluorescent 123-dihydrorhodamine dye during 3 h. The levels of ROS, when compared with control cells, largely and rapidly increased in the ADR plus X/XO cells, while in ADR group, it rose more gradually. Heat shock factor-1 (HSF-1) was the foremost transcription factor detected during the incubation time by electrophoretic mobility shift assay, first in the cardiomyocytes exposed to ADR plus X/XO and afterwards in the cardiomyocytes exposed to ADR alone. The activation of nuclear factor kappaB (NF-κB) followed the same time pattern, with onset in a longer incubation period. These results suggest that NF-κB transient activation in cardiomyocytes occurs when a threshold of ROS in the cells is reached, after which the activation signal is interrupted, while the activation of HSF occurred even before any differences were observed in ROS levels.

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W3 Alternative Approaches to Evaluating Immunotoxicity and Allergy

14
Alternative approaches to immunotoxicity and allergy testing

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For the evaluation of potential immunotoxicity/allergenicity of test materials (drugs, food ingredients/additives and industrial chemicals) in vivo testing is currently most relevant, especially because of the complexicity of the immune system including many different cell types, receptor interactions and signalling molecules. Despite this problem it is desirable also in this field of immunotoxicity/allergenicity testing to reduce, refine and replace the use of animals. Therefore the development, validation and acceptance of new in vitro alternatives for immunotoxicity and allergenicity testing (respiratory-, food and contact hypersensitivity) are needed. In particular in respect to for instance the implementation of the Registration, Evaluation and Authorisation of new and existing Chemicals (REACH) alternative in vitro/*in silico* testing methods and assessment strategies would be of importance to reduce laboratory use.

The objective of this presentation is to overview several approaches to in vitro immunotoxicity and allergy research as are presented in literature or subject of current research projects.

From the various in vitro approaches in respect to immunotoxicity and allergenicity testing it is evident that a lot of additional information can be obtained by using various types of cells such as lymphocytes, dendritic cells/langerhans cells, basophiles, etc., which also can be obtained from different species. However, it is also obvious that not for all interactions of immunotoxic compounds with the immune system in vitro methods can be easily developed like, e.g. for autoimmunity and immune stimulation. Overall the in vitro tests are extremely valuable for studying the molecular mechanism of action of immunotoxic/allergic compounds on target immune cells. It is evident, however, that in most situations in vitro alternatives only cover specific parts of the immunotoxic/allergic process and that in many cases they only can be used in conjunction with other data. Therefore, it is clear that despite the significant progress that is made with in vitro immunotoxicity/allergenicity testing still a lot of research is needed before in vitro tests will indeed be able to replace (in part) in vivo immunotoxicity/allergenicity testing.

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15
In vitro approaches to the assessment of immunotoxicity

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