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Introduction: Molecular imaging of stress and drug resistance (Chapter 3)

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Stress is a term for the broad spectrum of cell damaging circumstances influencing multiple cellular functions. Nowadays we already know that specialized biochemical pathways triggered by plenty of "stress-inducible factors", direct a cellular/tissue response depending on the kind and strength of stress. Although plenty of stress factors like irradiation, UV-light, extreme temperature changes, hypoxia, high blood glucose concentrations, drug delivery, etc. are well-known, the molecular mechanisms of the cellular response are still poorly understood. Since the human organism is almost permanently facing the influence of stress factors causing serious disorders (cardiovascular diseases, diabetes mellitus, cancer, etc.), the development of specific imaging systems is crucial for monitoring stress appearance, measuring its strength, imaging the specificity of drug delivery and the cellular/tissue response as a parameter of cellular stress or drug resistance.

To the most ubiquitous molecular events accompanying stress and drug induced cellular response belong inhibition of cell cycle progression, increased synthesis of free radical scavengers, induced expression of multi-drug transporters, triggering of inflammatory processes as well as programmed cell death and tissue remodelling. These molecular events can be frequently observed under birth asphyxia, neurodegenerative diseases, *diabetes mellitus* and tumor diseases which, therefore, represent favourable models for the development of disease specific imaging systems.

An optimal combination of *ex vivo* analytical, *in vitro* synthetic and *in vivo* imaging methods is a clue in the development of these systems. As an *ex vivo* optical analytical/imaging method "Comet Assay" provides the most complete information about the effect of DNA-damaging events (oxidative stress, etc.) and individual cellular responses (cell cycle control, DNA-repair, apoptosis, necrosis, etc.) perfectly supplementing an *in vivo* imaging information about apoptotic regions. For this imaging system the 99mTc-labeled annexin AV has been used as a specific marker which binds to phosphatidylserine – one of the "eat me" signals at the surface of the apoptotic cell.

The class of stress responsible metalloproteinases has recently been suggested as a potent group of markers for the molecular imaging of tissue remodelling induced by tumor and metastatic activity. MMP-2 (gelatinase A) degrades the basement membrane in surrounding cells. Increased expression of this enzyme has been detected in human colonic adenocarcinoma, whereas MMP-2 knockout mice have reduced angiogenesis and tumor progression capabilities. This gene is now under consideration as a potential marker for molecular imaging and has been imaged in a mouse model of breast cancer using an optical method. MMP-9 (gelatinase B) is known to be highly expressed in human breast cancer tissue. Downregulation of MMP-9 inhibits also glioma invasion *in vitro*.

The ABC-(ATP-binding cassette)-superfamily of transporters is a potentially important group of marker candidates for molecular imaging of drug resistance, since their up-regulation dramatically increases a simultaneous resistance of malignant cells to several anti-neoplastic agents that are structurally and functionally unrelated. This phenomenon is known as multidrug resistance. One example: the poor prognosis of glioblastoma patients is partially based on the minor success obtained from a chemotherapeutic treatment. Therefore, molecular imaging of drug delivery is essential for these patients in order to improve the efficiency of therapeutic approaches. New imaging approaches should be developed for these purposes.

An analysis of a stress and drug delivery dependent differential gene expression (transcriptomics and proteomics), concomitant selection of potential disease/state specific molecular markers, and a suitable labelling procedure of a bio-compatible probe dependent on the selected target are essential steps in the development of new targets and specific molecular imaging approaches *in vivo*.

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