complete tumor ablation in patients who could not have been cured with conventional surgical techniques.

Vessels walls are protected from over-heating by the intra-luminal blood flow that induces thermal dispersion, so that even lesions developping in the very vicinity of large vessels can be treated. No major complications have been reported with this technique. Results in the literature and personal datas will be reported and discussed. Special attention will be paid to imaging follow-up of the treated patients, for whom standard morphological analysis is not relevant.

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MR-guided percutaneous vacuum biopsy of breast lesions: Experiences with 100 cases

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Based on its excellent sensitivity MRI is able to contribute valuable additional informations for appropriate indications (posttherapeutic breast, preoperative patients, high risk patients). However, only part of the MR-dedected lesions prove to be malignant. So far MR-guided open surgery after MR-localisation and MR-guided needle biopsy are difficult procedures. By combining a new "breast biopsy coil" with a vacuum biopsy needle we have been able to percutaneously excise enhancing areas of up to 1.5 cm diameter based on MR-guidance. So far 99/100 procedures (performed under local anaesthesia) have been successful yielding malignancy in 25% of the cases and a definitive benign diagnosis in 75%. The procedure was well tolerated and proved very accurate as proven by reexcision of malignant lesions and MR-follow-up of benign lesions.

Value and future possibilities of this new method will be discussed.

Patentholder: S.H. Heywang-Köbrunner

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A TRAIL towards tumour therapy

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TNF Related Apoptosis Inducing Ligand (TRAIL) is a type II transmembrane protein that is capable of inducing apoptosis in a wide variety of transformed cell lines, but not normal cells, in vitro. A leucine zipper form of recombinant human TRAIL (LZ-huTRAIL) was created to promote and stabilize trimerization of this molecule, and purified recombinant LZ-huTRAIL was demonstrated to have potent biological activity in vitro. Extensive testing of human tumors to the cytotoxic effects of LZ-huTRAIL has shown that 57 of the 77 cell lines tested are sensitive to the cytotoxic effects of LZ-huTRAIL. Interestingly, although LZ-huTRAIL is potently cytotoxic to a wide range of human tumor cell lines, it is not toxic to normal human tissues in vitro, and failed to induce any detectable toxic effects in mice. To determine the potential therapeutic potential of LZ-huTRAIL in vivo a mouse xenograft model was established using the MDA-231 human breast adenocarcanoma in CB.17 SCID mice. The therapeutic potential of this molecule was demonstrated by the fact that repeated injections of LZ-huTRAIL not only suppressed growth of MDA-231 tumors, but also caused complete remission in a high proportion of the test subjects. In addition, the therapeutic potential of LZ-huTRAIL can be potentiated when used in combination with chemotherapeutic agents. Histologic examination of tumors from LZ-huTRAIL-treated SCID mice demonstrated clear areas of apoptois within 9–12 hours of injection, but manifest no apparent toxicities to normal tissues. These results indicate that TRAIL may have a substantial potential in therapy of human cancers.

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The role of mitochondria in apoptosis

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In response to most pro-apoptotic signal transduction pathways or lethal damage pathways, mitochondrial membrane permeability is compromised, leading to the disruption of essential mitochondrial functions and/or the selective release of soluble mitochondrial intermembrane (not matrix) proteins (SIMPs). Several among these SIMPs have potential apoptogenic properties: apoptosis inducing factor (AIF), because it can translocate to the nucleus where it causes chromatin condensation and large scale (50 kBp) DNA fragmentation; pro-caspases 2, 3, and 9 because they participate in the caspase activation cascade; and cytochrome c because it interacts with Apaf-1 to activate caspase-9. If these proteins, in particular caspases, become activated, they give rise to typical apoptotic cell death. In contrast, when caspases are inhibited (or when their activation is prevented due to the depletion of the Apaf-1 co-factor ATP), cells die from a bioenergetic catastrophe without acquiring the apoptotic morphology. What determines cell death thus is not always the action of SIMPs. Rather, cell death is determined by the underlying cause of SIMP release: mitochondrial membrane permeabilization. It appears that both anti-apoptotic Bcl-2-like proteins and proapoptotic Bax-like proteins act on mitochondria to inhibit or favor membrane permeabilization, respectively. These effects are, at least in part, mediated via interaction with sessile mitochondrial proteins from the permeability transition pore complex (PTPC). This scenario has important implications for the understanding of pathology-related dysregulations in apoptosis, as well as for the design of therapeutic strategies aimed at correcting such imbalances.

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Caspases and apoptosis

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Caspases are a family of aspartate specific cysteine proteases which contain an N-terminal peptide (prodomain), together with one large and one small subunit. Activation of caspases during apoptosis results in the cleavage of a wide array of cellular substrates which precipitates the dramatic morphological, and biochemical changes associated with apoptosis. Caspases can be divided into the "initiator" caspases (those caspases with long prodomains) and "effector" caspases (with short prodomains), such as caspases-3, -6 and -7. Caspase-8 is the most apical caspase in cell death receptor (CD95, TNF or TRAIL) induced apoptosis. Procaspase-9 is the most apical caspase in a post-mitochondrial caspase cascade. Procaspase-9 is activated following interaction with Apaf-1 in the presence of ATP/dATP and cytochrome c. We have now isolated an ~700 kDa caspase activating complex which contains Apaf-1, activated caspases -3, -9 and -7. Recently we have also shown that proteasome inhibitors induce apoptosis in B chronic lymphocytic leukaemia (B-CLL) cells and proteasome inhibitors result in the processing of caspases-3, -7, -8 and -9 prior to the activation of caspase-2. We propose that the proteasome inhibitors induce apoptosis in B-CLL cells by initiating a caspase cascade with caspase-9 as the "initiator" caspase. Thus, the defect in apoptosis in B-CLL cells appears to be in the signalling which regulates caspase activation, as the cells possess all the requisite caspases required for execution of the apoptotic program.

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Lipid mediators of apoptosis

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Cross-linking off surface "death" receptors induces apoptotic cell death in a variety of cell types. Two main biochemical pathways originate from receptors "death domain" to propagate the early apoptotic signals. A proteolytic cascade initiated by caspases, and sequential activation of phosphatidylcholine-specific phospholipase C (PC-PLC) and acidic sphingomyelinase (ASM), which results in ceramide accumulation. ASM-derived ceramide is then rapidly utilized for the neosynthesis of gangliosides. The transient accumulation of GD3 ganglioside, synthesized by the action of a2,8-sialyltranferase (ST8), is crucial for early recruitment of mitochondria to the apoptotic program. In fact, GD3 directly reduces loss of mitochondrial transmebrane potential, mitochondrial swelling, and release of reactive oxygen species and apoptogenic factors, including cytochrome c ad AIF. Genetic abrogation of the lipid pathway significantly prevents cell death. Therefore the PC-PLC/ASM/ST8 lipid pathway cooperates to the apoptotic program by contributing to the early mitochondrial damage.

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CD95, apoptosis pathways and cancer therapy

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Homeostasis in tissues is tightly regulated by cellular programs which control proliferation or apoptosis. Apoptosis may be induced by cellular receptors