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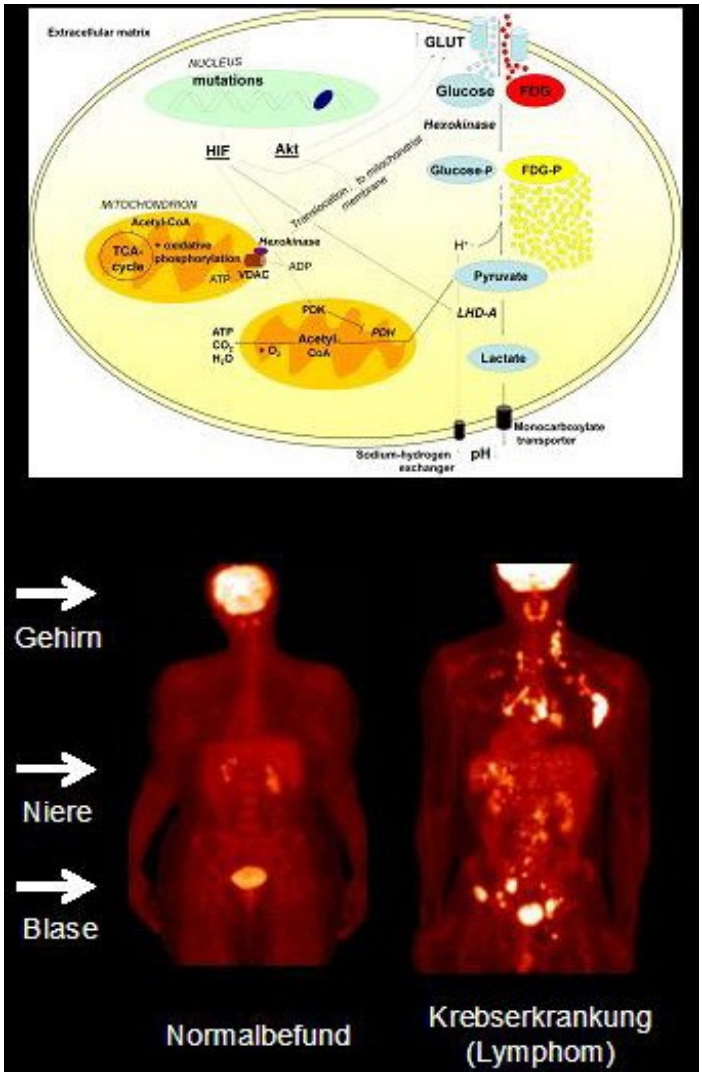
The cancer cells' sweet tooth might be their death sentence

Cancer cells are dangerous foodies. They metabolise far greater amounts of sugar than healthy cells. This was discovered by the Nobel Laureate Otto Heinrich Warburg, born in Freiburg, as many as 80 years ago. However, it has only been possible for nuclear medicine experts to make use of Warburg's findings on cancer cells' craving for sugar since the advent of modern positron emission tomography (PET). This has led to an improvement in the quality of cancer treatment. Professor Wolfgang Weber, who has been head of the Department of Nuclear Medicine at the University Hospital of Freiburg for the past few months, is a renowned PET expert.



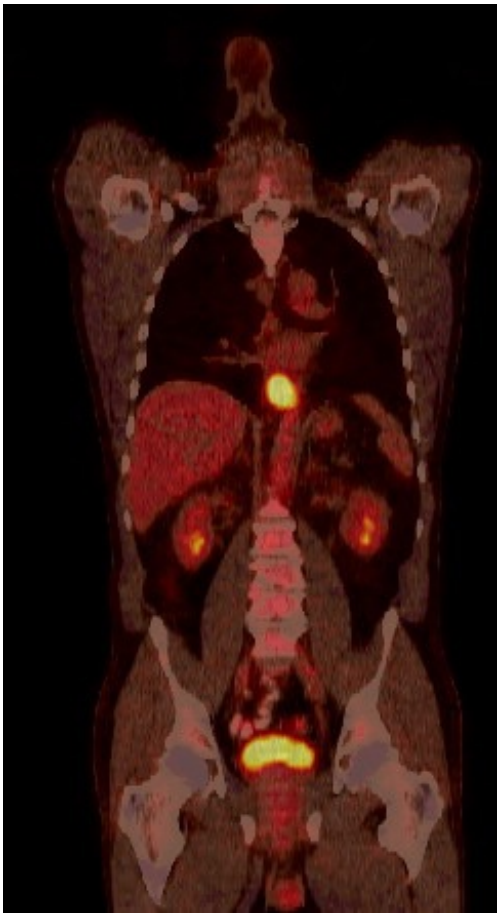
Identification of a lymphoma using PET (Photo: Work group Weber)

Tumours have a much higher sugar metabolism than healthy cells. “Nowadays, we know that the sugar metabolism varies considerably from tumour to tumour,” said Weber who returned from Los Angeles last year to take up the post as head of the Department of Nuclear Medicine at the University of Freiburg. By bringing Weber to Freiburg, the Freiburg University Hospital succeeded in attracting another highly renowned molecular imaging expert to its Department of Radiology. The researchers hope to take advantage of the tumour cells’ greed for sugar in order to starve the tumours out. However, the task is not as easy as it seems because the human brain is very quickly affected by an insufficient supply of energy. However, the tumour cells’ preference for sugar gives the nuclear medicine experts a reliable diagnostic property that quickly tells them whether a tumour reacts to a specific therapy or not.

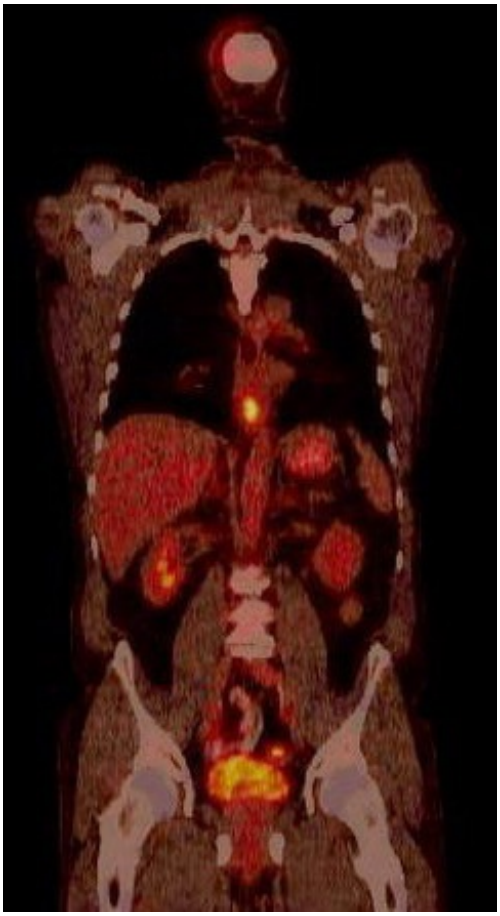
Positron emission tomography (PET)
PET is a nuclear medicine imaging technique that visualises the distribution of a weak radioactive substance in the body. This enables the body’s biochemical and physiological processes to be reconstructed. PET uses radionuclides that emit positrons. If a positron hits an electron, then antimatter combines with matter and energy is released. Two photons are released in opposite directions at an angle of approximately 180 degrees. This particularity enables the experts to pinpoint the precise spot in the body where decay has taken place. Gamma rays are detected with 20 to 30 detector rings and the projections provide images of the area where the injected radioactive substances have accumulated. PET was not originally intended for the identification and assessment of cancer, but for the monitoring of the metabolic rate of brain and heart.

The stronger the signal the more active the tumour

In the 1990s, PET's potential use in oncological applications was discovered. In order to assess the sugar metabolism of a tumour and its metastases, patients were injected with fluorodeoxyglucose (FDG). FDG is a glucose analogue and is taken up by glucose-consuming cells. However, small modifications, i.e. the addition of a phosphate group, prevents its metabolisation and FDG accumulates in the cell. The stronger the signal detected, the more active the tumour. If the signal becomes weaker or disappears completely, then the cancer cells have either ceased to grow or have been destroyed.



Sugar metabolism of an oesophagal tumour before…



… and after chemotherapy. (Photo: Work group Weber)

“PET enables us to assess very early on whether a cancer patient stands to benefit from a certain therapy or not and whether he or she will respond to a particular medication,” said Weber. This is particularly important in cases where drugs cause severe side effects. PET examinations are also recommended in cases where drugs are very expensive or are only effective in some patients. Newer oncological substances are a case in point, for example recombinant antibodies that dock to specific structures on the surface of tumours. However, not all tumours have the same structures. The coupling of an antibody to a specific surface structure induces tumour death; either the growth of the tumour cells is halted or the cells no longer receive blood supply. The best-known anti-cancer drug is the herceptin antibody that is effective in about one fifth of all breast cancer patients who have already developed metastases. New anti-cancer drugs also include antibodies against the EGF or VEGF receptors.

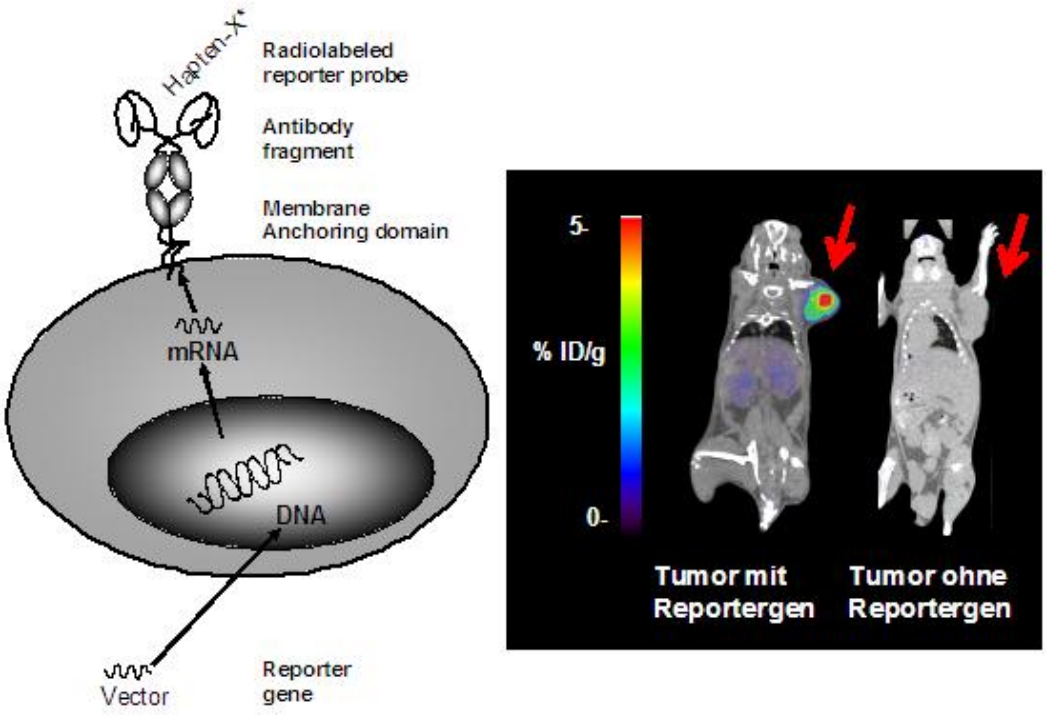
Irradiation directly in the tumour tissue

PET enables physicians to tell at a very early stage whether a tumour is adapting to the therapy. And to their great disappointment, the genetically instable cancer cells are often able to adapt to the therapy. A PET image shows quickly and reliably when the cells’ metabolism is no longer suppressed and their sugar consumption has once again increased.

Weber and his team are not only working on the clinical application of PET. One of their research projects focuses on the combination of molecular imaging and molecular cancer therapy. Initial results have already been obtained with neuroendocrine tumours, which are relatively rare. The physicians use radioactively labelled protein fragments, i.e. peptides that attach to the somatostatin receptor of these cancer cells. If enough of these receptors are available, then the tumour can be selectively irradiated with radioactively labelled peptides. However, this method is only effective if sufficient numbers of peptides are bound and retained by the tumour tissue. PET can be used to test whether the necessary prerequisites are in place for this type of therapy. The nuclear physicians can select patients that are suitable for therapy with radioactively labelled peptides and determine the most effective peptide dosage.

“Reporter genes” provide information

“Our goal is to transfer this interesting principle to other, more common types of tumours,” said Weber who has already discovered interesting candidates that might be targets for the radioactively labelled peptides: integrins. Integrins are a family of adhesion molecules that are formed by many body cells. However, some integrins are only produced when new blood vessels are formed to supply the tumour with nutrients. The work group is aiming to optimise the molecules that bind to and recognise these integrins so that they accumulate in different tumours and release radiation dosages that are high enough to actually damage the cancer cells.



In mice, "reporter genes" already give away the location of the tumour. (Photo: AG Weber)

Another of Weber's exciting projects deals with the development of reporter genes. These genes are introduced into a cell and integrated in the cell's genome, thereby providing the physicians with important information about the cell, including information on whether the cells are alive, whether the cells actually are there where they should be and about the cells' particular function at a certain point in time. The scientists envisage the use of reporter genes to assess the outcome of stem cell therapy. A foreign gene is integrated into a cell which then synthesises an artificial receptor in a configuration that is unable to bind substances that are naturally produced in the body. The scientists further hope to engineer a molecule that docks specifically to this artificial binding site. "If we label this molecule with radioactivity, then PET will enable us to discern whether transplanted stem cells are still alive or whether they have arrived at the desired location," said Weber. In the best case, the physicians will also be able to determine the cells' functions. However, before this will be possible, the scientists will have to place the reporter gene at a particular site in the genome, so that it will only be expressed and transported to the cell surface when the cell performs a certain activity.

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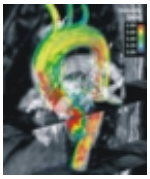

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