Breast cancer: a few millilitres of urine to diagnose the disease early

It would be phenomenal news if it turned out that breast cancer could be detected by way of urine samples. Treating physicians would be able to use conspicuous test results to begin further examinations as quickly as possible along with therapy if necessary. Prof. Dr. Elmar Stickeler and his team from the Freiburg University Medical Centre have developed a method that identifies the composition of microRNAs in urine. They were able to predict with over 91 percent accuracy whether a tumour was present or not. They have now filed a patent for the method.

The earlier breast cancer is detected, the better the chance of recovery. 71,000 new cases of breast cancer are reported in Germany every year, and numbers are rising. Statistically, one woman in eight contracts the disease. Although breast cancer is more common in industrialised countries, the mortality rate is much higher in Asia and Africa due to poorer diagnosis and treatment. Breast cancer accounts for one third of all cancers in women and even though the likelihood of recovery is relatively good, it remains the most common cause of cancer-related deaths. 17,000 women die of breast cancer in Germany every year. The causes and risk factors for breast cancer are quite diverse. In addition to alcohol, nicotine and lack of physical activity, factors a woman can influence herself, genetics plays a major role in certain breast cancers. There is also evidence that administration of female hormones such as progestogens and estrogens to treat the symptoms of menopause increases the risk of breast cancer. When there are so many possible causes of breast cancer, standardised therapies do not make much sense.

Prof. Dr. Elmar Stickeler and his team are working on simplifying early identification of breast cancer.
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"Breast cancer is a very heterogeneous disease," says Prof. Dr. Elmar Stickeler from Freiburg University Medical Centre. "So we can't use the same therapy for all patients." All possible factors need to be taken into consideration in order to adapt treatment to individual requirements. This usually involves different types of treatment, including surgery, chemotherapy, hormonal and radiation therapy. Immunotherapies using monoclonal antibodies that are specifically directed against cancer cells are increasingly being used. More than eighty percent of breast cancers are randomly discovered by patients themselves. However, the problem is that once tumours are palpable, they have already reached a certain size and are already at an advanced stage, which carries a relatively poor diagnosis. Ultrasound and mammography are the best way of localising tumours, after which tissue biopsies can be taken to assess whether a tumour is malignant or benign. Breast cancer-related mortality could be reduced by 25 percent if tumours could be identified at a much earlier stage than currently possible.

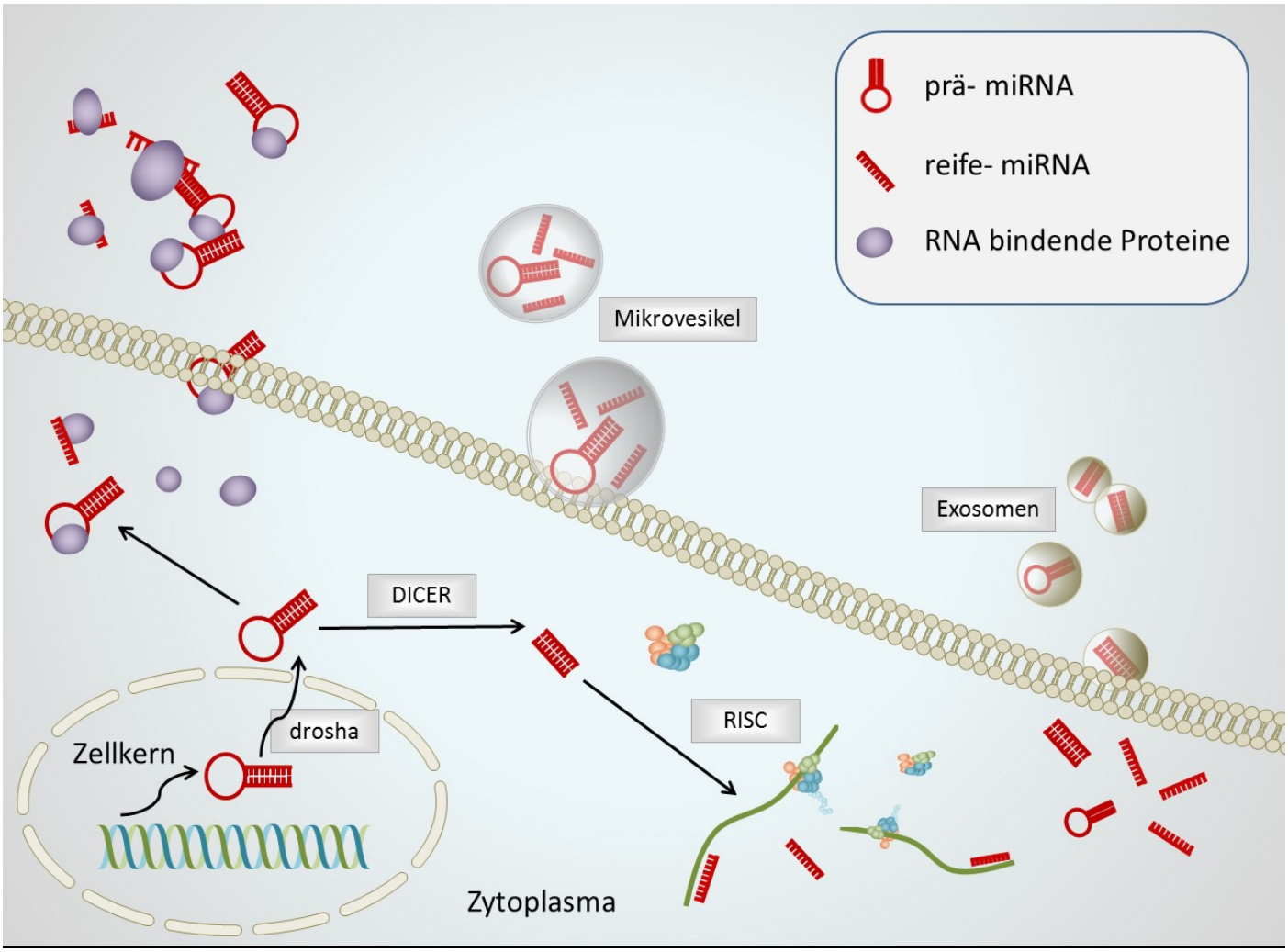
MicroRNAs as biomarkers

But how can breast cancer be detected via urine? Stickeler and his team carried out a study in which they analysed the urine of volunteers for the presence of small molecules known as microRNAS (miRNAs). These tiny fragments are non-coding RNAs and are increasingly attracting the interest of biomedical researchers due to findings that suggest the important part they play in the regulation of genes on the post-transcriptional level. Although little is yet known about the exact biological function of miRNAs, there is substantial evidence to show that they play a major role in regulating the cellular metabolism. miRNAs are 21 to 23 nucleotides long. The expression of around 20 to 30 percent of all human genes is regulated by miRNAs; a given miRNA might target many different messenger RNA (mRNA) molecules. In turn, a certain target might be regulated by several miRNAs. Around 2000 human miRNAs are known and have been shown to play an important role in intercellular communication and the suppression of cellular transformation events such as the formation of tumours. In addition, miRNAs control and maintain the pluripotency of embryonic stem cells.

Altered miRNA expression has been shown to enhance cancer-forming processes. miRNAs act together with transcription factors in a regulatory network and may have an activating or inhibitory effect, depending on the number and type of miRNAs and targets involved. As 70 diseases have already been associated with the dysregulation of miRNAs, it is believed that they could be very interesting for developing disease-related biomarkers.

Role of miRNAs in cancer

miRNA expression was associated with cancer for the first time in 2002. Since then, dysregulated miRNA expression has been found in blood plasma and different tumours, including brain tumours, melanomas and breast cancers. miRNAs obviously play a role in carcinogenesis since they modulate the expression of tumour suppressor genes or inhibit apoptosis. "Or they activate oncogenes. However, in either case they support oncogenic function," says Stickeler. The reasons for miRNA dysregulation are probably quite diverse and not just limited to one gene. "Cells are far more complex than we believed up until now. We are always discovering something new," says the scientist. "We have come to the stage where we are able to describe what is happening." Special combinations of dysregulated miRNAs have been associated with breast cancer and are already used as blood biomarkers for this disease. Stickeler and his team have also discovered a specific miRNA expression pattern in the urine of breast cancer patients. They investigated 24 healthy women and 24 women who had recently been diagnosed with breast cancer. They found that the expression levels of four specific miRNAs were significantly different in the diseased and healthy women. They were either up- or downregulated. Using this urinary miRNA signature, the researchers were for the first time ever able to predict with 91 percent accuracy whether a woman had a breast tumour or not. The data were consistent with the blood and serum miRNA signatures of breast cancer patients. "If we are able to



MicroRNAs play a bigger role in cellular events than previously thought. DICER, Drosha and RISC are enzymes/enzyme complexes that are involved in miRNA processing (DICER, Drosha) and modulating the efficiency of miRNA regulation (RISC).

confirm in a broader study that breast cancer patients have different miRNA profiles than healthy women, we will be able to show that our tool is suitable for predicting the presence of a tumour," says Stickeler.

Non-invasive method

The use of urinary miRNA signatures would be an attractive tool for the diagnosis of breast cancer as it is a non-invasive method for detecting circulating miRNAs. The results will, of course, always have to be substantiated with in-depth medical examinations. Stickeler says that mammography will continue to be needed in the future. He does not think that replacing existing methods makes sense. "Only pathologists can make reliable diagnoses from tissue biopsies. You can only see under the microscope whether a tissue sample is cancerous or not," explains Stickeler. He is careful to stress that if his new method turns out to be broadly applicable, more detailed diagnoses will always be needed to substantiate the initial prediction.

"I regard the method as a potential supplement to existing methods as it is a relatively easy way to find out whether a conspicuous, cancer-related miRNA signature is present," says Stickeler. Further examinations will be necessary to find out whether the tumour is malignant and where exactly it is located. Stickeler believes that the method is an excellent screening tool and also suitable for monitoring treatment progress. The researchers are now planning to recruit larger patient groups to substantiate their findings and test the tool's potential to differentiate between breast cancer subtypes and whether the urinary composition of the molecules changes as the disease progresses. This would then show whether the method is also suitable for monitoring treatment progress.