Tumour monitoring using liquid biopsy

Liquid biopsy, the analysis of cancer biomarkers and circulating tumour cells in body fluids such as blood, is revolutionising the diagnosis and monitoring of cancer. It has also been possible to expand circulating tumour cells from the blood under laboratory conditions. It is expected that in the future, liquid biopsy will be able to precisely characterise tumour cells at every stage of a cancer.

Rows of test tubes for liquid biopsy.

The ability to diagnose cancer in internal organs and monitor disease progression based on the analysis of easy-to-collect blood or urine specimens has long been on doctors' wish lists. Tumour cells that circulate in the blood of cancer patients, so-called circulating tumour cells (CTCs), have been shown to be promising liquid biopsy material for detecting cancer. However, detecting CTCs requires high analytical reliability (for example, the genome sequencing of single cells), which has only become possible in recent years through advances made in the methodologies used. Over the same time period, researchers have also discovered freely circulating tumour DNA (so-called ctDNA) and microRNAs (miRNAs, i.e. short, noncoding RNA sequences that regulate gene expression) in the blood of cancer patients, which can serve as tumour-associated biomarkers.

In addition, these DNA fragments can be used to detect tumour-specific mutations or gene fusions, and the DNA methylation patterns can be analysed for the presence of tumour-associated epigenetic changes. Exosomes (vesicles that are budded off by certain cells, including cancer cells) that are present in the blood serum and in which nucleic acids, proteins and other signalling molecules of the primary tumour cells can be detected, also represent valuable diagnostic targets for cancer diagnosis.

A body fluid sample that is used for cancer diagnosis is called "liquid biopsy". Liquid biopsies are less costly and risky than traditional biopsies involving the removal of tissue for diagnosing cancer. Liquid biopsy has become a highly dynamic field of research and is revolutionising the diagnosis and monitoring of tumours in the field of oncology (see "Liquid biopsies – beacons of hope for cancer diagnosis?").

Possible liquid biopsy sources (body fluids) as well as cell structures that are suitable for tumour biopsy.

In addition to blood and urine, body fluids such as saliva, fluid from the lungs (pleural effusions) or so-called brain water (cerebrospinal fluid) are other sample types that can also be used for liquid biopsy. These types of samples are especially important for diagnosing brain tumours, as the above-listed tumour-characteristic cell components are usually not able to pass through the blood-brain barrier. However, blood is by far the most important source for liquid biopsies, and also the most advanced as far as clinical application is concerned. This is demonstrated below using the diagnosis of breast cancer as an example.

Circulating tumour cells in cell culture

The fact that CTCs can be found in the blood of breast cancer patients long after the primary tumour has been surgically removed has been known for over 15 years. In 2013, scientists from Heidelberg led by the stem cell researcher Andreas Trumpp and his former colleague Irène Baccelli were able to provide experimental proof that there is a - very small - cell population among CTCs that can actually form metastases (so-called "metastasis-initiating cells"; see "Experimental evidence of stem cells for metastasis").

These metastases, as well as recurrences (tumours returning after successful initial treatment), often have properties that differ considerably from those of the primary tumour. For example, they are resistant to chemotherapeutic agents that were effective in the primary tumour. Tumour cells need to be monitored using molecular biology techniques to be able to adapt therapy to a patient's requirements, including over prolonged treatment periods. However, removing several tissue biopsies is

a heavy burden for the patient. Moreover, the small tissue samples usually only contain a very small amount of tumour material, which is generally not sufficient for long-term monitoring.

Prof. Dr. Andreas Trumpp, head of the Division of Stem Cells and Cancer at the German Cancer Research Center and director of HI-STEM gGMbH

Trumpp, who was awarded the prestigious Baden-Württemberg Research Prize for Excellence in Applied Research in December 2018, reported at a press workshop on metastases on 21 January 2019 that his research groups at the DKFZ and HI-STEM ("Heidelberg Institute for Stem Cell Technology and Experimental Medicine") had for the first time successfully expanded CTCs obtained from the blood of breast cancer patients under cell culture conditions. Thus, the blood-derived tumour cells can be used to study the molecular (e.g. multi-omics), genetic (e.g. mutational profiles) and biological (e.g. MIC, therapy resistance) characteristics of tumour cells in greater detail. In addition, the expanded CTCs and the cancer stem cells they contain are available for preclinical testing to assess the efficacy of various drug combinations with the goal of identifying new, effective therapies for individual patients.

The HI-STEM "Liquid Biopsy" platform has the potential to provide researchers with access to well-characterised live tumour cells from sequential blood samples for every stage of breast cancer – before, during and after therapy, and possibly also during tumour remission as well as before and after cancer recurrence. This will help uncover tumour cell resistance mechanisms and potentially also expand treatment options for advanced breast cancer patients.

No "global sensation" as yet!

On 21 February 2019, the German newspaper BILD ran the following cover story: "…[we report exclusively that] researchers at the University Hospital in Heidelberg have developed a blood test that for the first time ever reliably detects breast cancer. A global sensation!" Christoph Sohn, medical director of the University Women's Hospital at Heidelberg University Hospital, stated that a liquid biopsy test known as "HeiScreen" was developed under his leadership and was able to detect even small tumours in blood samples of women with breast cancer using 15 different biomarkers (miRNA and methylation markers). He also reported that the plan was to bring the test to market maturity and into the clinic through HeiScreen GmbH, a spin-off from Heidelberg University Hospital, by early 2020. However, until now no details have yet been published in peer-reviewed scientific journals. The press release stated that the test had a sensitivity rate of 60 percent for over-50s (and a higher sensitivity rate in young breast cancer patients, which is a smaller group), but made no mention of the rate of false positives obtained with healthy women from the blood test. Moreover, at the time the news was published, less than half of the planned 2,000 patients had participated in the clinical study. It therefore comes as no surprise that experts strongly criticised the publication of the test results in a tabloid. On 5 April 2019, even the supervisory board of Heidelberg University Hospital decided in a special session to commission a high-level external commission "to deal with the matter comprehensively and swiftly."

Although the commission may come to the conclusion that the finding is not a global sensation, informing the general public at such an early stage shows at least that liquid biopsy is a very topical issue in research and that high expectations are riding on it. As far as clinical oncology applications are concerned, reliable liquid biopsy tests will not be long in coming.

Article

16-Apr-2019
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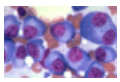

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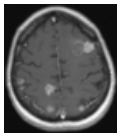

Tumour metastasis

With molecular diagnostics to biomarker-based personalised therapy

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