A biomarker as indicator for the likelihood of developing aggressive prostate cancer

Overexpression of the protein BAZ2A, which leads to alterations in epigenetic patterns, increases the malignant properties of tumour cells, including their mobility and their ability to form metastases. The findings of a team of researchers from Heidelberg, Zurich and Hamburg may have led to the discovery of an urgently needed prognostic biomarker that would make it possible to differentiate aggressive prostate cancer from the less malignant form.

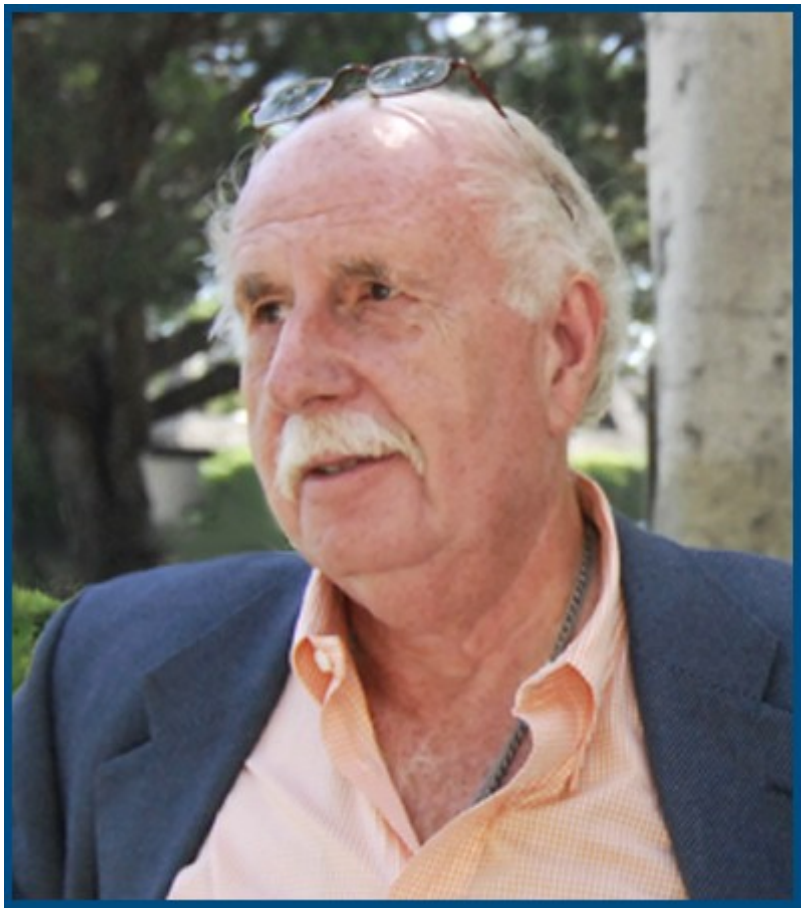
Over 60,000 men are diagnosed with prostate cancer in Germany every year and 10,000 to 15,000 die from its consequences. Prostate cancer is thus the most common form of malignant cancer and the second most common cause of death from cancer in men in Germany. As prostate cancer mainly occurs in men over 50, these figures are expected to double over the next twenty years due to demographic changes. In general, the earlier cancer is detected, the better the chances of treating it. Regular cancer screening to find unsuspected cancers is therefore recommended for the relevant age groups. However, prostate cancer is in a class of its own.

On close inspection, it seems that cancerous cells are present in almost all men over 50. However, only a few have prostate cancer symptoms. Most prostate cancers never pose a problem. They grow relatively slowly, and do not reduce life expectancy even when left untreated. Systematic investigations of deceased men have shown that prostate cancer cells were present in around 30 percent of all men over 50, and that by the age of 80, the vast majority of men have some cancer in their prostate glands. Only a very small number of men develop aggressive cancers where cells invade other parts of the body (metastasis) and therefore require medical treatment. The question therefore remains as to whether slow-growing low-risk prostate cancers can be differentiated from aggressive cancers that are associated with a greater risk of death.

So far, there is no reliable answer to this question. Urologists around the world recommend what is called a PSA test, i.e. a blood test that measures the amount of prostate-specific antigen (PSA). However, the test is strongly contested because it does not provide any information about the aggressiveness of the cancer (see text box below). In a study published in the renowned journal Nature Genetics, a team of scientists from Heidelberg, Zurich and Hamburg reported a feature that correlates with the degree of prostate cancer malignancy. This discovery could be the much sought-after biomarker that can differentiate between malignant and non-malignant forms of prostate cancer.

Prof. Dr. Christoph Plass, director of the Department of Epigenomics and Cancer Risk Factors, German Cancer Research Center, Heidelberg.

The prostate cancer methylome



Prof. Dr. Richard S. Ablin, discoverer and critic of the PSA test
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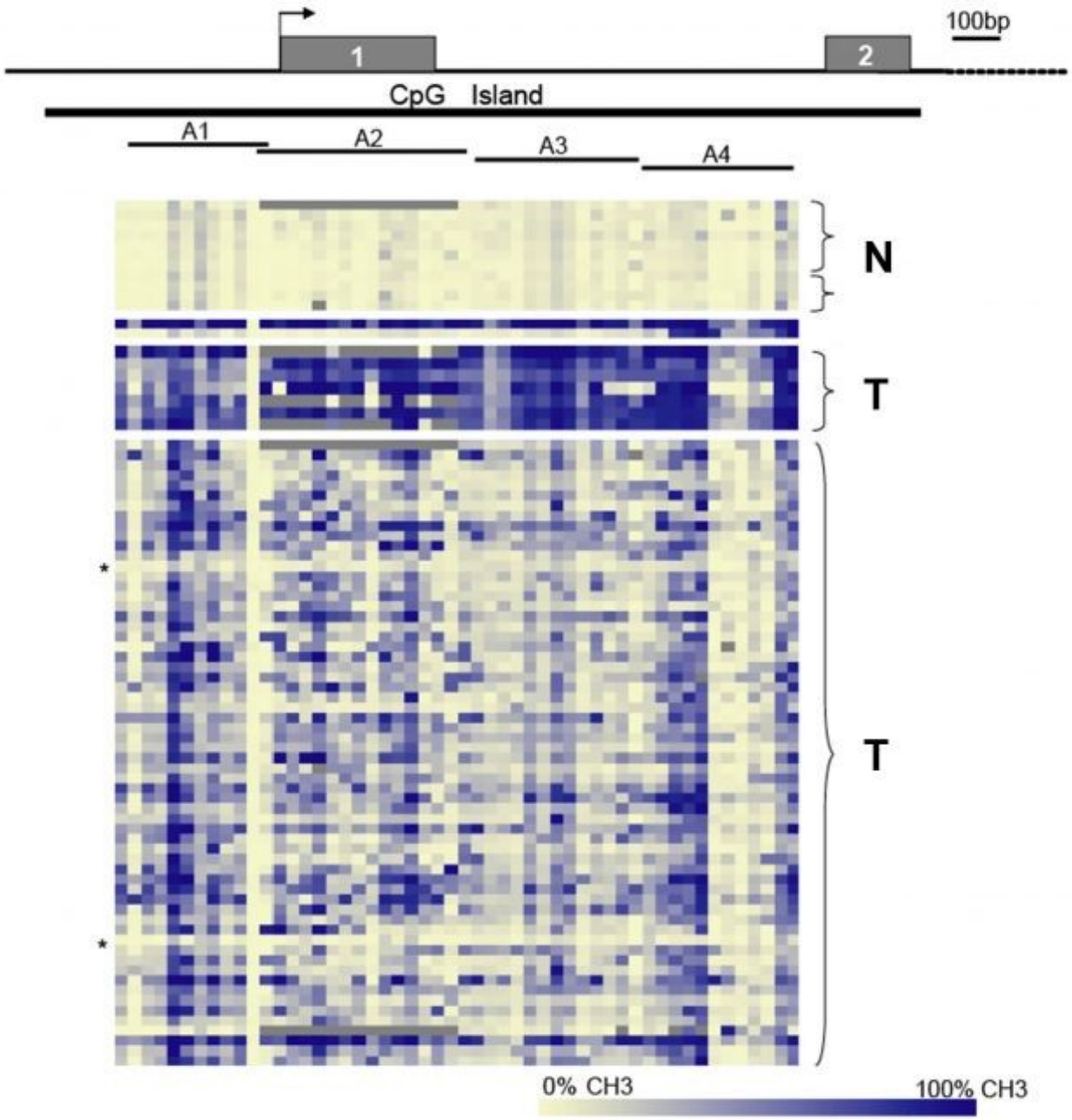
While most advanced, aggressive tumours are characterised by a large number of different genetic defects, prostate cancer exhibits far fewer mutations than other types of cancer. "We have therefore tended to suspect that prostate cancer is driven primarily by alterations in epigenetic characteristics, that is, chemical changes in the genetic material that do not affect the sequence of DNA building blocks," says Prof. Christoph Plass from the German Cancer Research Center, who is one of the project leaders in the current publication. Genes can be switched on or off by way of epigenetic modifications such as the methylation of the DNA base cytosine. Although the modifications do not alter the underlying genetic code, they can nevertheless be passed on from one daughter cell to the other as the cells divide. Around eight percent of all human genes undergo epigenetic changes. Epigenetic modifications are particularly common in cancer cells. However, the means by which epigenetic patterns in cancer cell DNA undergo changes have remained elusive for a long time. Plass and his colleagues analysed the DNA sequences of several thousand tumour tissues stored in relevant databases and discovered many mutations in epigenetic regulatory proteins. These mutations have the potential to specifically deregulate hundreds of genes.

In their latest study on prostate cancer, the researchers systematically investigated the methylome, i.e. the overall number of methylations in the genome. They found that the methylations are not randomly distributed in the genome; instead, there are so-called differentially methylated DNA regions that are common to almost all prostate tumours. In the search for reasons for the different methylation patterns of healthy and tumour cells, the scientists came across a known regulatory protein called BAZ2A. This protein was known to silence ribosomal RNA genes, which reduces the viability of cells due to the suppression of ribosome production.

Paradoxically, BAZ2A promoted uncontrolled cell growth, which is characteristic of cancer cells. When



Quantitative DNA methylation of the promoter region of the DAPK1 gene. N = healthy tissue; T = tumour tissue. The methylation frequency ranges from 0 % (light yellow) t0 100 % (dark blue). DAPK1 ("death-associated" protein kinase 1) is an enzyme of the apoptosis signalling pathway.
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BAZ2A was turned off, cancer cell growth slowed. The researchers found that higher levels of BAZ2A increased specific malignant properties of prostate cancer cells, including their mobility and their capacity to invade surrounding tissue. This suggests that the overproduction of BAZ2A had an effect on malignancy and capacity to metastasise.

The molecular profiling of tumour cells showed that BAZ2A regulates numerous protein-coding genes and interacts directly with EZH2 (another epigenetic regulatory protein), coordinating the repression of genes frequently silenced in metastatic prostate cancer. The analysis of 7,682 tissue samples obtained from prostate cancer patients showed that the higher the BAZ2A levels in the tissue were, the more advanced the tumour was at the time of diagnosis, and the more frequently it had spread and formed metastases. The researchers also found that BAZ2A expression correlated

with elevated PSA levels resulting from recurrences and metastases.

Plass said that BAZ2A seems to have a direct effect on the metastatic potential of tumour cells and can therefore serve as a valuable predictor of disease progression. This still needs to be clinically confirmed. However, the finding suggests that the biomarker is suitable for differentiating aggressive prostate cancers from those with a low risk.

The predictive value of the PSA test

Prostate-specific antigen (PSA) is an enzyme that is secreted into the seminal fluid of the prostate. The American pathologist and discoverer of PSA, Richard S. Ablin, has repeatedly pointed out that PSA is a tissue-specific rather than a cancer-specific enzyme. Ablin therefore considers any threshold value taken as an indication of cancer as arbitrary. An increased PSA level (e.g. 15 ng/ml) does not necessarily mean that a man has prostate cancer, whereas someone with a low PSA level (3 ng/ml) might have prostate cancer. The serum PSA levels are not elevated in around 50% of all men with prostate cancers and in around one third of all invasive forms of prostate cancer.

However, an increase in PSA levels over a longer period is a warning sign and should be closely monitored. The University of Heidelberg recommends that PSA levels are measured in conjunction with annual medical examinations such as ultrasound diagnostics and physical checks (see link on the right-hand side). No-one disputes that the PSA test is useful for diagnostic purposes, for example as a biomarker for identifying potential recurrence and metastasis after surgery.

Whether PSA screening should be routinely used for early detection of cancer is currently a major controversy. While the American PLCO trial was unable to prove survival benefit for patients who have undergone PSA testing as part of normal prostate cancer screening measures, the European ERSPC trial found that the PSA test reduced the probability of dying of prostate cancer by 20 percent – alas with a "high risk of overdiagnosis", which means that the test quite often mistook harmless tumours for malignant ones. This then meant that the men concerned underwent surgical treatment that had life-changing effects such as impotence and incontinence. According to the ERSPC trial, 1,410 men had to be tested and an additional 48 prostate cancer cases treated in order to save a single life by way of PSA screening.

The bitterness of the controversy surrounding PSA screening is due to the business interests associated with the test; more than 30 million men have already undergone PSA testing in the US. In his recently published book ("The Great Prostate Hoax - How Big Medicine Hijacked the PSA Test and Caused a Public Disaster"; Palgrave Macmillan 2014), Ablin vehemently calls for the "inappropriate use of PSA screening of men over 50 to be stopped. Doing so would save billions of dollars and prevent millions of men from having to undergo unnecessary debilitating treatments each year." The German statutory health insurance scheme does not cover the costs of the PSA test as part of preventive screening measures, but does cover costs for men who are suspected of having prostate cancer or who are undergoing prostate cancer treatment.

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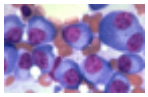

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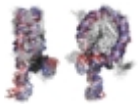

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