In vitro tests show that clinically tested drug overcomes resistance to potential new cancer therapy

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Results from laboratory experiments carried out by a team of molecular biologists at Saarland University have identified a strategy for overcoming resistance to a new therapeutic opportunity for prostate cancer patients and for potentially suppressing the migration of cancer cells. The new therapeutic approach, which is currently being studied by numerous research groups, aims to destroy cancer cells by influencing cellular calcium distribution. However, the research team, supervised by Professor Richard Zimmermann and Dr Markus Greiner, found that in about half of the patients examined, a cellular mechanism was present that could impede the efficacy of the new therapy. The molecular biologists discovered that this resistance was caused by an increased concentration of the protein Sec62 in the tumour cells. Results from their laboratory cell line experiments indicate that a pharmaceutically active agent previously used in the treatment of psychotic disorders can counteract the observed cellular resistance as well as supress cell migration. The research team has published its findings in the medical journal *BMC Cancer*.

Prostate cancer is the most common malignant tumour in men. A new therapeutic approach to combating the disease is currently the subject of international research. In recent years, US scientists have developed a number of analogues of thapsigargin that are capable of selectively killing tumour cells by emptying the calcium stores in these cells. But recent research by scientists at Saarland University's Faculty of Medicine

in Homburg has demonstrated that in approximately half of the patients suffering from prostate cancer, the tumour cells can be expected to show a resistance to this new form of therapy. 'The resistance mechanism is due to a higher concentration of the protein Sec62,' explains Professor Richard Zimmermann. As a result of increased Sec62 levels the protein calmodulin can close the calcium leak channels more efficiently in the membrane of the important intracellular calcium store known as the endoplasmic reticulum. 'This is why tumour cells with a higher concentration of Sec62 show greater resistance to treatment regimens based on thapsigargin analogues,' says Zimmermann.

Working with tumour cell cultures in the laboratory, Zimmermann's group at the Department of Medical Biochemistry and Molecular Biology has found a possible solution to the problem and their results have been published in the journal *BMC Cancer*. 'Using tumour cell lines, we were able to show that a substance called trifluoperazine (TFP) was able to counteract the observed resistance. TFP has been used as an antipsychotic and was marketed in Germany under the brand Jatroneutral® where it was used in the treatment of psychotic disorders,' explains Dr Markus Greiner, a member of Professor Zimmermann's research team. 'TFP binds directly to the protein calmodulin and thus impairs the calmodulin-mediated closure of the calcium channels,' explains Greiner.

Sec62 has been shown to be an important tumour marker, i.e. a protein that occurs at enhanced concentrations in tumour cells, not only in prostate carcinomas, but also in thyroid and lung carcinomas. The Homburg researchers see a correlation between the presence of Sec62 protein and a more aggressive tumour and hence lower patient survival rates. The research team also measured increased Sec62 concentrations in tumours that had already metastasized. 'Calcium is an important signalling molecule that regulates cell migration, which is itself an important contributor to tumour metastasis,' says Markus Greiner. The

calcium in the cells ensures that the cells can detect the direction in which they are migrating. If these tumour cells are treated with TFP, the calcium store will be emptied and the cells essentially lose their orientation. 'This leads to an almost complete cessation of cellular migration,' explains Greiner.

'We propose a therapeutic approach based on TFP in combination with thapsigargin analogues. In future, this may be a therapeutic option for those many patients whose tumours have a high cellular concentration of Sec62, which might make them unsuitable for treatment with thapsigargin,' says Greiner. The results obtained by the Homburg research team will now be evaluated in tumour model studies before any clinical trials can be proposed.

More information: Linxweiler M., Schorr S., Schäuble N., Jung M., Linxweiler J., Langer F., Schäfers H.-J., Cavalliè A., Zimmermann R., and Greiner M.: "Targeting cell migration and Endoplasmic Reticulum stress response with calmodulin antagonists: Mimicking Sec62-depletion phenotypes by small molecule treatment," *BMC Cancer*, 2013, 13:574; DOI: 10.1186/1471-2407-13-574

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