Scientists discover way to block growth of prostate cancer cells

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Scientists have discovered for the first time a specific biochemical pathway by which the sex hormone, androgen, increases levels of harmful chemicals called reactive oxygen species (ROS) in the prostate gland that play a role in the development of prostate cancer.

They found that a drug that blocks this pathway significantly prolonged survival and inhibited tumour development in mice that were genetically engineered to spontaneously develop prostate cancer and die of the disease. The hope is that this drug could be used eventually to treat men at high risk of developing prostate cancer and to prevent recurrences in men already treated for primary tumours.

Dr Hirak Basu told a news briefing at the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Prague today (Wednesday 8 November): “Previous work has demonstrated that androgen treatment increased reactive oxygen species levels in androgen-dependent prostate cancer cells, but, until now, the pathway involved was unknown.”

Dr Basu is an associate scientist and principal investigator in the Prostate Cancer Group at the Paul P. Carbone Comprehensive Cancer Center, Madison, WI, USA. He and his collaborators at the centre found that levels of a key enzyme, spermidine/spermine acetyl transferase (SSAT), which starts oxidation of polyamines, rose markedly when prostate cancer cells were treated with androgen. Polyamines are small molecules produced in large quantity by the prostate gland and are secreted in the

seminal fluid. Oxidation of polyamines generates a large amount of the ROS, hydrogen peroxide. Peroxide causes oxidative stress, a condition in which cells produce an excess of oxygen-free radicals, which are known to play a key role in cell signalling and prostate cancer development.

“These results demonstrate that polyamine oxidation is one of the major causes of androgen-induced oxidative stress in prostate cancer cells,” said Dr Basu. “The discovery of this pathway is a major step forward in understanding the role of androgen in prostate cancer development.

“Many scientists in the polyamine field have worked towards increasing, rather than decreasing, oxidative stress in order to destroy established tumours. However, no one that I know has tried to reduce oxidative stress by blocking polyamine oxidation to prevent prostate tumours, and this is what we set out to do.”

Having discovered the role played by polyamine oxidation, the researchers with the help of their collaborators at Wayne State University, Detroit, MI, USA, synthesised a molecule called MDL 72,527 (MDL), which was previously known to be an inhibitor of acetyl polyamine oxidase (APAO). APAO catalyses the oxidation of acetyl polyamines produced by SSAT – the process that results in the generation of ROS. MDL can, therefore, block androgen-induced ROS production in prostate cancer cells.

They injected MDL into the genetically engineered mice and found that it inhibited polyamine oxidation and reduced oxidative stress in the prostate glands of the animals. The treatment significantly increased overall survival and delayed time to prostate tumour development. In repeat experiments, between 50-60% of mice treated with MDL survived ten to twelve weeks longer than the untreated control group.

“To the best of our knowledge, this is the first report of a specific

enzyme inhibitor MDL that blocks androgen-induced oxidative stress in the prostate and prevents spontaneous prostate tumour development," said Dr Basu.

More tests have to be carried out, but the researchers, working with the world-renowned prostate cancer clinician Dr George Wilding (a co-author of the paper), hope that phase I clinical trials of MDL might be able to start in 12-18 months.

Dr Basu said: "After surgery and radiotherapy for the primary tumour, breast cancer patients can be treated with several drugs such as tamoxifen and aromatase inhibitors that prevent or delay breast cancer recurrence. No such treatment exists for prostate cancer patients. After treatment of their primary tumours, prostate cancer in men is managed by watchful observation only. The immediate goal of our research is to develop agents such as MDL to fill this unmet medical need. If MDL, or any of the other agents that we are working with, can be expanded further to treat all high-risk men, we will be delighted."

Source: European Organisation for Research and Treatment of Cancer