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'Jekyll-and-Hyde' protein offers a new route to cancer drugs

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The mood changes of a 'Jekyll-and-Hyde' protein, which sometimes boosts tumour cell growth and at other times suppresses it, have been explained in a new study led by Oxford University researchers.

The researchers in Britain, with collaborators in Singapore and the USA, carried out a comprehensive biological study of the protein E2F, which is abnormal in the vast majority of cancers. They were able to explain the dual natures it can take up in cells in the body, and indicate how it could be a potent target for developing new cancer drugs.

The Oxford University scientists have since carried out a drug-discovery screen, and shown that compounds which block the protein's change into 'Mr Hyde' result in the death of cancer cells.

'This mechanism for switching a key protein is very novel. Nothing else I've come across behaves like it,' says Professor Nick La Thangue of the Department of Oncology at Oxford University, who led the work. 'Subtle changes in terms of the chemistry of the protein have dramatic and polar opposite effects on the tumour cell, either allowing them to continuously grow or switching them to cell death mode.

'We are excited by this new discovery, which provides a new and very important approach to developing new types of cancer drugs. We have much work to do,' says Professor La Thangue.

The researchers from the University of Oxford, the Genome Institute of

Singapore and the University of Texas' MD Anderson Cancer Centre in the USA report their findings in the journal *Molecular Cell*. The study was part-funded by the UK Medical Research Council and Cancer Research UK.

Cells in the body go through cycles of growth and division, pauses and death in a highly regulated way. Cancer involves the breakdown of these controls leading to unlimited expansion of the cells in a growing tumour.

The protein E2F is inextricably linked to cancer. It is normally tightly controlled in the cell cycle, but in most if not all cancer cells the processes E2F oversees go awry so that it keeps cells growing.

Puzzlingly, while it can be a factor driving cancer, on other occasions E2F is protective and removes damaged cells. When normal cells experience damage, E2F is involved in switching the cell towards cell death in a process called apoptosis. This helps prevent the build up of DNA errors and the development of cancer.

It's this dual Jekyll-and-Hyde nature of E2F that the researchers have been able to explain for the first time.

They show that E2F is an important switch that determines cell fate. As Dr Jekyll, when DNA damage is detected, it leads to cell death. As Mr Hyde, it switches on cell growth and proliferation – and in most if not all cancers, it is this function of E2F that becomes out of control.

The researchers show that two enzymes compete to attach a molecular label, or flag, on different parts of the E2F protein. The flag in one position sees E2F act to cause cell death and the same flag in another position see E2F boost cell growth and proliferation.

Professor La Thangue says: 'It's like there's an angel and a devil

competing to get on each shoulder of the protein. Which one gets the upper hand is able to whisper in the ear of the protein and tell it what it should do. With the molecular flag on one shoulder, E2F goes into cell kill mode. With the flag on the other, it goes into cell growth mode. The challenge is to mimic this process with drugs, and reinstate the death pathway in tumour cells.'

In cancer cells, E2F gets stuck with the flag boosting growth and division, helping drive the tumour's growth. The researchers identified another protein in the cell which looks for the presence of this flag.

'Blocking this protein means the devil's whispers never get heard and E2F doesn't transform into Mr Hyde,' says Professor La Thangue. 'Instead, E2F switches over to cell-death mode and the cancer cells die out.

'We've identified compounds – drug candidates - that do exactly that,' he explains.

Dr Shunsheng Zheng, first author of the study and a graduate student on the joint A*STAR-University of Oxford DPhil scholarship programme, said: 'E2F is a tricky protein to work with. Normal cells use it for growth, cancer cells need it for hypergrowth, but too much of it seems to drive cancer cells into suicidal mode.'

Dr Kat Arney, science information manager at Cancer Research UK, which part-funded the work, said: 'Cancer is a complex biological problem, and getting to grips with the molecules that drive it is essential if we're to find new cures. Although there's a lot more work to be done before this new discovery could become a treatment for patients, this research is an important step forward in understanding E2F's 'split personality' in both driving and destroying cancer cells.'

More information: The paper 'Arginine methylation-dependent reader-writer interplay governs growth control by E2F-1' is to be published in the journal *Molecular Cell* on Thursday 26 September 2013.

Provided by Oxford University