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Positive feedback and tumorigenesis: A vicious circle that promotes cell proliferation

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Cancer cells are essentially immortal. The acquisition of an unlimited capacity to divide – the process of immortalization - is a central event in the genesis of tumors. Normally, cells are subject to stringent mechanisms which control their proliferation. Together these ensure that pre-malignant cells are induced to enter a senescent, non-dividing state or to undergo apoptosis, i.e. commit suicide.

A research team led by Professor Heiko Hermeking and Dr. Antje Menssen from LMU's Institute of Pathology has now discovered how the regulatory protein c-MYC subverts these controls, thus facilitating the growth of tumors. High levels of c-MYC, which are present in most tumor cells, activate SIRT1, an enzyme that inhibits both senescence and apoptosis. The new results show that the two proteins actually form a positive feedback loop, in that SIRT1 also promotes the activity of c-MYC. Normal cells avoid this vicious circle because they keep the gene that codes for c-MYC turned off, unless they receive growth-promoting signals. In tumor cells, this mechanism no longer functions and the cells can proliferate unchecked.

Their latest findings have implications for cancer treatment, as Menssen explains: "Our results indicate that tumor types in which c-MYC plays a crucial role, such as lymphomas and colon or breast cancers, should be especially susceptible to pharmacological inhibitors that interrupt the feedback loop. In particular, combinations of drugs that interact with different components of the loop could provide a new route to effective therapies of these malignancies." (*PNAS* 19.-23.12)

The c-MYC protein is involved in the control of many basic biological functions, including cell growth and division. It is therefore vital for processes that require cell proliferation, such as embryonic development and the generation of all the cell types in the blood. Overproduction of c-MYC, on the other hand, can have lethal consequences for the organism. Continuous synthesis of c-MYC is a prominent feature of immortalized cells, which divide in an uncontrolled fashion and thus facilitate the formation of tumors. Normally, multiple mechanisms serve to regulate the expression of the gene for c-MYC, and keep the level of the protein present in cells within appropriate limits. In essence, the gene is activated only when a cell is instructed to do so by specific growth-promoting signals. If this failsafe mechanism is disabled, a second internal system switches in. This back-up circuit ensures that increased concentrations of c-MYC cause premature cell senescence (which makes cells unresponsive to growth signals) and induce programmed cell death. However, in tumor cells, these safeguards no longer function – and in some tumors and cell types it has emerged that c-MYC itself is responsible for knocking them out. "How c-MYC achieves this has remained largely unclear," says Hermeking. In order to clarify the mechanisms involved, the researchers focused on the enzyme SIRT1 as a possible accomplice of c-MYC. As Hermeking explains, "SIRT1 seemed to us a likely candidate because a related enzyme has been shown to play a role in extending the lifespan of cells in lower organisms. In human cells, SIRT1 is known to inhibit a regulator that promotes senescence and programmed cell death."

The hunch turned out to be correct, since the team, which included molecular biologists from Aachen University and the Karolinska Institute in Stockholm, was able to show that c-MYC actually enhances SIRT1 function in a number of different ways. First, it activates NAMPT (nicotinamide phosphoribosyltransferase), which is responsible for the synthesis of a molecule required for the action of SIRT1. Secondly, c-MYC represses an inhibitor of SIRT1, so releasing a further

brake on its function. Finally, SIRT1 itself potentiates these effects by reducing the rate of degradation of c-MYC. The end result is a positive feedback loop which drives the continuous accumulation of both SIRT1 and c-MYC in the cell.

The c-MYC protein is synthesized in large amounts in most tumors. Furthermore, in certain cancers, such as lymphomas and cancers of the colon and the breast, c-MYC is known to play a causative role in the origin of the primary tumor. In these cases, mutations in the c-MYC gene itself, or in genes that regulate its expression, result in constant production of the c-MYC protein. The new findings are thus of particular relevance for the development of new treatment options for these types of cancer, since one would expect them to be highly sensitive to direct inhibition of SIRT1 or NAMPT. Interestingly, several studies in recent years have revealed that levels of NAMPT are also increased in many tumors. Indeed, a chemical inhibitor of NAMPT is already undergoing clinical trials. "Our study strongly suggests that the feedback loop initiated by excess c-MYC drives the overproduction of NAMPT. A combination of drugs that would allow us to inhibit the actions of both SIRT1 and NAMPT might therefore have a synergistic effect and could open up new therapeutic possibilities," Menssen points out.

In addition, the new findings raise questions regarding the allegedly positive effect of a daily glass of red wine on lifespan. The putative health benefits of this regime have been attributed in part to the activation of SIRT1 by the compound resveratrol, which is found in red wine. Indeed, commercial development of pharmacological SIRT1 activators such as resveratrol is already underway – in the hope that they will slow the aging process and block the development of obesity and diabetes. In this context, Hermeking advises caution: "In the light of our results, these agents should only be used after further extensive study."

More information: The c-MYC oncoprotein, the NAMPT enzyme,

the SIRT1 inhibitor DBC1, and the SIRT1 deacetylase form a positive feedback loop. A. Menssen, P. Hydbring, K. Kapelle, J. Vervoorts, J. Diebold, B. Lüscher, L.- G. Larsson, H. Hermeking. *PNAS* Early Edition 19.-23.12.2011 doi: 10.1073/pnas.1105304109