The good, the bad and the ugly: The many roles of c-JUN in cancer

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The process of cell division is tightly regulated, as mistakes may lead to cancer. The so-called c-JUN protein has been fingered as causing tumors in both skin and liver. The group of Veronika Sexl at the University of Veterinary Medicine, Vienna, has now uncovered a surprising detail with the discovery an additional function of c-JUN's also prevents silencing of an important anti-tumor factor. The results have recently been published in the open-access journal *Oncotarget*.

The c-JUN protein was initially described in the late 1980s as the mammalian equivalent of a protein responsible for causing cancer in birds. Intense research in a number of labs has subsequently led to a basic understanding of how the protein works. c-JUN is a transcription factor that modifies (phosphorylates) key regulatory proteins in the cell, thereby activating or deactivating them and leading to unregulated cell division and hence cancer. It has also become clear that c-JUN acts not on its own but in conjunction with an array of further proteins that modulate its function.

Karoline Kollmann in the group of Veronika Sexl, now at the University of Veterinary Medicine, Vienna, recently discovered an additional activity of c-JUN. Together with her collaboration partners at the Medical University of Vienna and in Madrid, she showed that c-JUN can bind to the promoter of a kinase gene, known as Cdk6, thereby preventing the gene from being inactivated (by means of methylation). The result is increased activity of Cdk6, which further stimulates cell division. c-JUN only activates transcription of Cdk6 in cancer cells,

where it makes the disease progress even faster. Kollmann's work was published in April in the journal *Blood* (2011, Vol. 117, pp. 4065-4075).

The surprising aspect of the discovery is that the "new" function of c-JUN is independent of the protein's normal activity. Kollmann has now added a further twist to the tail with the discovery that c-JUN protects not only the Cdk6 gene – thereby accelerating tumour formation – but also the p16 gene. p16 is a known tumour suppressor gene and its mutation or inactivation is associated with an increased risk of contracting a variety of forms of cancer. By protecting its promoter from inactivation, c-JUN seems to be helping the cells to fight the cancer.

Does this mean that the main villain of the piece is not actually as bad as we thought? Kollmann's response is fairly guarded. "I think it means that the functions of all these proteins are far more complex than we know. They all work together with many other proteins and the overall effect probably depends on a large number of factors. We have a lot more to learn before we can understand what proteins to inhibit to treat the disease."

More information: The paper "c-JUN prevents methylation of p16INK4a (and Cdk6): the villain turned bodyguard" by Karoline Kollmann, Gerwin Heller and Veronika Sexl was recently published in Oncotarget (Vol. 2 No. 5). impactjournals.com/oncotarget/ … article&op=view&path%5B%5D=279&path%5B%5D=432

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