Researchers associate two oncogenes with the agressiveness and incidence of leukaemia in mice

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Proteins regulating cell division determine tumour growth. Ongoing clinical trials are currently studying inhibitors for two of these proteins, Cdk4 and Cdk6, targeting several types of cancer, such as breast cancer, lung cancer and leukaemia. The Cell Division and Cancer Group at the Spanish National Cancer Research Centre (CNIO), led by Marcos Malumbres, has discovered the molecular mechanism behind the interaction of these proteins. Researchers also demonstrated in mice that the simultaneous inhibition of both molecules is more effective than the individual inhibition. The study has been published this week in the medical journal *Blood*.

"Cdk4/6 inhibitors used in cancer treatment don't differentiate between the two molecules. The effectiveness of blocking both proteins at once has not been demonstrated to date," explains Malumbres.

To get a wider perspective on this issue, Malumbres and his team specifically designed genetically modified mice carrying active Cdk4, active Cdk6, or both versions of the active proteins. The study, which was carried out in collaboration with the Medical University of Vienna, demonstrated that the simultaneous activation of both proteins promoted tumour growth leading to more aggressive tumours and an increased risk of developing leukaemia.

"The assumption to date has been that these molecules act independently

of each other, however, our recent findings now suggest that the combined inhibitors could be a more effective cancer treatment," says Malumbres.

Researchers also explain why the simultaneous activation of both oncogenes leads to such aggressive tumours: under normal conditions, their activity is inhibited by p16INK4A proteins; but when both Cdk4 and Cdk6 are present in high levels, p16INK4A proteins are unable to act as a retaining wall, leading to uncontrolled tumour growth.

In 2013, Cdk4 and Cdk6 inhibitors were designated "Breakthrough Therapy" by the United States Food and Drug Administration (FDA), for their potential to double life expectancy in breast cancer patients. Some pharmaceutical companies have shown interest in these inhibitors, whose efficiency is already being evaluated in other types of cancer, including lung cancer and melanoma.

"The clinical success of these compounds depends on the appropriate selection of patients. Our findings could help us to understand the molecular basis underpinning the success of these inhibitors, thereby contributing to the development of novel and more effective drugs," states Malumbres.

More information: Cdk4 and Cdk6 cooperate in counteracting the INK4 family of inhibitors during murine leukemogenesis. Rodríguez-Díez E, Quereda V, Bellutti F, Prchal-Murphy M, Partida D, Eguren M, Gómez de Cedrón M, Dubus P, Cañamero M, Martínez D, Sexl V, Malumbres M. *Blood* (2014). DOI: 10.1182/blood-2014-02-555292

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