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Not the protein, but its location in the cell, determines the onset of leukemia

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Scientists are still searching for the cause of many forms of Leukemia, including T-cell acute lymphoblastic leukemia. VIB researchers connected to the Katholieke Universiteit Leuven have discovered that the carcinogenic property of the fusion protein NUP214-ABL1 largely depends on its location in the cell. Casting new light on the biological processes behind T-ALL, this finding is important in the search for new targeted therapies that are less toxic than chemotherapy.

The white blood cells in our body combat foreign intruders, such as viruses and bacteria. However, in leukemia, the formation of white blood cells is disturbed: the cells that should develop into white blood cells multiply out of control without fully maturing. This process disrupts the production of normal blood cells, making patients more susceptible to infections. T-ALL, a particular form of leukemia, is the most prevalent cancer in children under 14 years of age and occurs predominantly between the ages of two and three. At the moment, with an optimal treatment using chemotherapy, over half of the children are cured. But scientists hope to be able to develop targeted therapies that are less toxic than chemotherapy, based on knowledge of the biological processes behind T-ALL.

Oncogenes are often at the root of cancer. So, scientists around the world are concentrating on identifying oncogenes and their related proteins. Recent research by Kim De Keersmaecker and colleagues in Jan Cools' research group (VIB-K.U.Leuven) indicates that the location in the cell where these proteins are found plays an important role in the

entire carcinogenic mechanism. In collaboration with Maarten Fornerod (Nederlands Kanker Instituut, Amsterdam) and Gary Gilliland (Harvard Medical School, Boston), the VIB researchers have demonstrated that NUP214-ABL1, a fusion of two proteins, is carcinogenic only when it is in a protein complex near the nucleus of the cell. Located at another place in the cell, NUP214-ABL1 does not lead to cancer. This finding sheds new light on the study of carcinogenic processes.

Many forms of cancer are caused by genetic defects in which a certain kinase becomes too active – and this is the case with NUP214-ABL1. The most obvious solution is to make the carcinogenic kinase inactive, and so kinase inhibitors are usually used to combat these kinds of cancers. However, the carcinogenic kinase often becomes resistant to these inhibitors – which is certainly true for T-ALL. So, scientists are actively seeking alternative approaches.

De Keersmaecker's recent research results now offer a possibility. Indeed, the scientists have shown in cells that NUP214-ABL1 is no longer carcinogenic when it cannot bind with the protein complex in the vicinity of the cell nucleus. On the basis of these results, the researchers want to further investigate the therapeutic possibilities of compounds that render binding between the complex and NUP214-ABL1 impossible. This study also indicates that the location of proteins can play an important role in other forms of cancer/leukemia as well.

Source: VIB (the Flanders Institute for Biotechnology)

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