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# Malignant bone marrow disease: New hope for MPN patients

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Myeloproliferative neoplasms (MPNs) are still difficult to treat. A team from Vetmeduni Vienna and the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences/Medical University of Vienna has discovered a new therapeutic approach that could fundamentally change this situation, as evidenced by a study that was published recently in the academic journal *Blood*.

MPNs are a group of rare, malignant diseases of the bone marrow involving the production of an excess of red blood cells, white blood cells and/or platelets. MPNs are chronic diseases with only 1 to 2 new cases diagnosed per 100,000 people every year. MPNs can affect people at any age, but they are most common among adults around 60 years old. Men have a slightly higher risk of developing the disease compared to women.

MPNs are caused by genetic changes (mutations) of the hematopoietic cells in the bone marrow that are acquired spontaneously, due to certain genetic predispositions or as a result of environmental influences. Over 80% of patients with MPNs exhibit an acquired point mutation in the gene JAK2. This so-called JAK2V617F mutation causes JAK2, a regulator of cell proliferation, to be constantly turned on. As a result, the affected cell begins to divide out of control—and the illness takes its course.

MPN patients have so far been treated with ruxolitinib, a JAK2 inhibitor. Ruxolitinib effectively controls the symptoms but does not

offer a cure, as the malignant stem cell clone is located in the bone marrow and is generally not attacked. Discontinuing the treatment involves a high risk of relapse or progression to AML, a form of leukaemia. Therefore, it is of importance to discover new therapeutic approaches.

## Significant factor influencing the disease: the protein CDK6

A research team led by Veronika Sexl from Vetmeduni Vienna and Robert Kralovics from CeMM/Medical University of Vienna succeeded in doing just that. Using a mouse model, they identified the protein CDK6 as an important factor influencing the development of JAK2V617F-initiated MPN. "We were able to show that in the absence of CDK6, the proliferation of affected stem cells was reduced and cell death was increased. As a consequence, the absence of CDK6 ameliorated the clinical symptoms and increased life expectancy," says Sexl.

## Novel therapeutic approach for MPN patients

The absence of CDK6 clearly attenuates the symptoms in the long term. The spleen, greatly enlarged by the disease, shrinks back to its normal size and the progression of the disease is delayed. Kralovics: "CDK6 is a central signalling node that connects cell cycle control; the activation of the protein NFκB, a master regulator of inflammation; apoptosis, which refers to the programmed cellular death; and malignant stem-cell function. Our work indicates that fine-tuning the level of CDK6 influences this mechanism and could potentially improve the quality of life of MPN patients. This opens up the possibility of a completely novel therapeutic approach."

**More information:** Iris Z. Uras et al, Cdk6 coordinates Jak2V617F mutant MPN via NFκB and apoptotic networks, *Blood* (2019). DOI: 10.1182/blood-2018-08-872648