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Jak of all trades? Not of leukaemia therapy

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About one in five or six cases of adult leukaemia in Western populations relates to so-called chronic myeloid leukaemia, or CML. Treatment of CML usually relies on inhibitors of the abnormal protein that causes the condition but some patients do not respond to treatment and efforts are underway to develop a supplementary approach, targeting the so-called JAK2 kinase. Recent results from the groups of Veronika Sexl at the University of Veterinary Medicine, Vienna (Vetmeduni Vienna) and Giulio Superti-Furga at the Research Center for Molecular Medicine of the Austrian Academy of Sciences (CeMM) have called this strategy into question. The work is published in the current issue of the prestigious journal *Nature Chemical Biology* and is of immediate relevance to leukaemia treatment.

The cause of CML has been known since 1960, when two scientists in Philadelphia, Pennsylvania showed that the disease was associated with a particular genetic abnormality, the "Philadelphia chromosome". Philadelphia chromosomes represent the result of an incorrect crossing-over between two chromosomes, through which part of the Bcr ("breakpoint cluster region") gene from chromosome 22 fuses with the Abl gene on chromosome 9. The fusion gene product is a tyrosine kinase, i.e. it can phosphorylate other proteins on tyrosine residues. When it does so, it incorrectly activates several signal pathways controlling cell division in white blood cells and leads to leukaemia. Thankfully, drugs have been developed that prevent the kinase activity of the BCR-ABL fusion protein and the majority of patients treated with such tyrosine kinase inhibitors (e.g. imatinib) show no further signs of leukaemia.

Unfortunately, however, patients may develop resistance to the therapy so an alternative approach is required. Recent developments have focused on the use of drugs targeting another kinase involved in CML, the JAK2 kinase. In normal white blood cells, JAK2 is known to activate a further molecule, known as STAT5, which is absolutely required for the development of CML. The argument runs that if JAK2 could be specifically inhibited – and thus STAT5 not activated – it would bring fresh hope to patients who do not respond to treatment with imatinib. Several potential inhibitors of JAK2 are currently undergoing clinical trials and may shortly be available for treating patients.

The theory is appealing but to date we do not really understand exactly what happens when JAK2 is inactivated following the initiation of leukaemia by the Bcr-Abl oncogene. Sexl and her colleagues have used a transgenic mouse model to clarify the functions of these proteins in leukaemia. Their results were highly unexpected. The JAK2 kinase was found to be not required for the maintenance of the disease, i.e. inhibiting JAK2 in leukaemic cells had no therapeutic benefit. However, inhibition of STAT5 in leukaemia was sufficient to prevent cell proliferation. As Sexl says, "this means that the normal signalling pathway is completely rewired in CML cells: STAT5 activity no longer depends on JAK2." In support of this conclusion, the researchers were able to show that the BCR-ABL protein directly phosphorylates STAT5, thereby activating it.

As Superti-Furga notes, "The findings have extremely important consequences for CML therapy in humans," adding, "We are very happy that the collaboration between our two groups is so fruitful". Put bluntly, leukaemia patients that do not respond to imatinib will not be helped by inhibiting JAK2. Interestingly, some JAK2 inhibitors do slow the progression of leukaemic cells, although they must be given at very high levels. The "therapeutic" action is mediated by a secondary target of the JAK2 inhibitors, which Sexl and colleagues have shown to be the Bcr-

Abl oncogene itself. Sexl concludes that, "at the moment there is simply no rationale for giving leukaemic patients JAK2 inhibitors. If we want to help patients who do not respond to imatinib, we should concentrate instead on developing inhibitors to STAT5."

More information: dx.doi.org/10.1038/NChemBio.775