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'If Hamlet give the first or second hit': The development of Burkitt's lymphoma

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The human c-myc gene encodes a transcription factor (MYC) involved in the regulation of a vast number of other genes – it has been estimated that the transcription of about one in six genes is somehow under the control of MYC. Perhaps because of MYC's wide range of targets, mutations of the c-myc gene are frequently associated with a variety of tumours, not only with Burkitt's lymphoma. Mutations that lead to excessive amounts of the MYC protein are particularly threatening.

It has long been known that Burkitt's lymphoma only develops when MYC is mutated or overexpressed, although experiments in mice have shown that some animals live quite happily and healthily with higher levels of the MYC protein. This observation is consistent with the "second hit" model for the origin of cancer: as well as a change to c-myc, a second gene must also be disturbed before disease is initiated. In the case of lymphomas, the second hit is often in the p53 or the Bcl2 gene. Loss of p53 or increased amounts of the BCL2 protein are both associated with lymphoma. But how does the course of the disease relate to the nature of the second hit?

This question has now been investigated by Sexl's and Stoiber's groups. Using a mouse model of human lymphoma, the scientists compared the effects on the immune system of deleting the p53 gene or over-activating the Bcl2 gene, or both. The results were dramatic. If the p53 gene was mutated, the resulting tumours were no longer recognized and killed by the mouse's immune system. In other words, such tumours escaped the mouse's normal "surveillance" mechanism and went on to cause full-

blown lymphoma. On the other hand, if instead the Bcl2 gene was overexpressed (to produce more BCL2 protein), the mouse's immune system could recognize and attack the tumour cells, thereby slowing or preventing cancer development. If both the p53 and the Bcl2 genes were affected, immune recognition remained efficient, in other words the Bcl2 effect is dominant.

The results show for the first time that the nature of the "second hit" determines whether the animals are able to mount an immune response against the developing lymphoma. Interestingly, Sexl's collaboration partner Ulrich Jäger from the Medical University of Vienna has obtained preliminary data from human patients that are consistent with the results in mice. The collaboration shows once again the value of comparative medicine in understanding the progression of human diseases.

The findings have extremely important consequences for tumour therapy in humans. First, because of the association of high BCL2 levels with tumour development, a number of pharmaceutical companies are currently developing BCL2 inhibitors for use in cancer therapy. As Sexl points out, though, "The inhibitors may have the unwanted effect of preventing the natural immune reaction. It will be important to evaluate the consequences of BCL2 inhibition carefully – taking the host immune system fully into account – to ensure that the drugs have no harmful side-effects." Secondly, the results may potentially shape future immunotherapeutic approaches, as whether a tumour overexpresses Bcl2 or does not express p53 clearly has a dramatic influence on the course of disease.

More information: The paper, "The cooperating mutation or 'second hit'" determines the immunologic visibility toward MYC-induced murine lymphomas," by Christian Schuster, Angelika Berger, Maria A. Hoelzl, Eva M . Putz, Anna Frenzel, Olivia Simma, Nadine Moritz, Andrea Hoelbl, Boris Kovacic, Michael Freissmuth, Mathias Müller, Andreas

Villunger, Leonard Müllauer, Ana-lris Schmatz, Berthold Streubel, Edit Porpaczy, Ulrich Jäger, Dagma Stoiber and Veronika Sexl is published in the current issue of the journal *Blood* (2011, 118(17):4635-45).