Inhibited Tyk2 retains anti-cancer activity

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Tyrosine kinase 2 (Tyk2) is an enzyme involved in intracellular signalling and has an important role in activating the immune system. But enzymatically active Tyk2 can also promote excessive immune reactions and growth of certain cancer types.

Since several years, scientists are developing substances to specifically inhibit the kinase activity of Tyk2 for the treatment of inflammatory diseases and for potential use in cancer therapy. However, complications may occur: Tyk2 crucially contributes to the maturation and activation of natural killer (NK) cells. NK cells form part of the innate immune system and are the first defence against virus infections and cancer. They recognise cancer cells and produce a series of proteins capable of destroying them. Inhibition of Tyk2 could therefore also weaken NK cells and block an important front of the body's own defence against cancer.

First evidence of kinase-independent functions of Tyk2 in a living organism

A team of researchers led by Birgit Strobl, Mathias Müller and Veronika Sexl from the Institute of Animal Breeding and Genetics and the Institute of Pharmacology and Toxicology at the Vetmeduni Vienna investigated cancer growth in Tyk2 gene-targeted mice.

Tyk2-deficient mice were not able to control cancer growth. NK cells of these animals exhibited incomplete maturation and were unable to destroy cancer cells. Surprisingly, in mice whose Tyk2 was present but enzymatically inactivated, cancer growth was strongly suppressed and NK cells retained their ability to kill the cancer cells.

Project leader Birgit Strobl explains: "Until now, it was unknown that Tyk2 has effects within the whole organism that do not depend on its enzymatic activities. Without its kinase activity, it still drives NK cell maturation and boosts their activity. Here lies the key for cancer medicine. Drugs that inhibit the kinase activity of Tyk2 – and there are currently several of them in the testing phase – do not hamper the immune system in its work. These drugs are therefore even more promising for cancer therapy than previously thought."

More information: "In vivo tumor surveillance by NK cells requires TYK2 but not TYK2 kinase activity" *OncoImmunology*. DOI: 10.1080/2162402X.2015.1047579

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