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New line of approach for combination therapy against melanoma

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A melanoma is a malignant form of skin cancer and is one of the most aggressive types of tumors there is. Treatment is particularly difficult, because melanomas are usually resistant against conventional chemotherapy treatments. Agnieszka Gembarska and Chris Marine

(VIB/KU Leuven) have found a new line of approach in which to treat these aggressive skin cancers, namely by combating the interaction between the protein MDM4 and the tumor suppressor p53. Their research offers a new angle for the development of medication and confirms that combination therapies - including those using the recently developed BRAF inhibitors - hold the promise of further improvement of the clinical response to a treatment. This study was published in the authoritative journal *Nature Medicine* and will undoubtedly be followed with interest by the pharmaceutical industry.

Chris Marine: "Our results are important on two levels. From a scientific perspective, it is very important that we have been able to prove that p53 plays a key role in the formation of melanomas. However, this research also offers perspectives for optimizing the existing treatment strategies for melanomas. The current treatment with BRAF inhibitors has positive effects on nearly 80% of the patients, but many of them relapse after a few months. We may have discovered a way of preventing this relapse".

p53, MDM4 and the formation of cancer

Chris Marine and his team has a long standing interest in p53 - a master

tumor suppressor protein (in other words a protein that counteract the formation of cancer). Mutations in the p53 gene are very common in many various types of cancer. Surprisingly, mutations in p53 are (almost) never seen in melanomas. Scientists suspected that melanomas had found an alternative way of bypassing the action of p53.

The protein MDM4 has a negative effect on the action of p53 and has been the scientific focus of the VIB investigators for many years. Agnieszka Gembarska and Chris Marine have now demonstrated that (65% of) melanomas contain much higher concentrations of the MDM4 protein than normal cells. The scientists found a pharmacological way to inhibit the interaction between MDM4 and p53 and were thereby able to restore the tumor suppressive effect of p53 in melanoma cells.

Chris Marine: "The restoration of the p53 activity in the melanoma cells makes these cells more susceptible to chemotherapy and the BRAF inhibitors. In our research, we were able to identify MDM4 as a very promising target for treatment of melanoma, as part of a combination therapy.

Provided by VIB (the Flanders Institute for Biotechnology)

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