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Press Release

Virility drug may boost skin cancer growth

Tübingen biochemists discover signaling pathway in melanoma cells affected by erectile dysfunction drug Sildenafil

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Tübingen researchers have found indications that taking the drug Sildenafil can stimulate the growth of skin tumors. Sildenafil is used to treat erectile dysfunction and is the active ingredient in a number of drugs which have been on the market since the late 1990s. Sildenafil is now also contained in a number of generic products for the treatment of erectile dysfunction. Professor Robert Feil and his working group at the University of Tübingen's Interfaculty Institute of Biochemistry demonstrated in animal experiments and human cell cultures that Sildenafil appears to have a stimulating effect on the messenger molecule cyclic guanosine monophosphate (cGMP) – which in turn promotes the growth of existing malignant melanomas. Interference with the cGMP pathway in melanoma cells could possibly be used to treat skin cancer. The results of the study are published in the latest edition of *Cell Reports*.

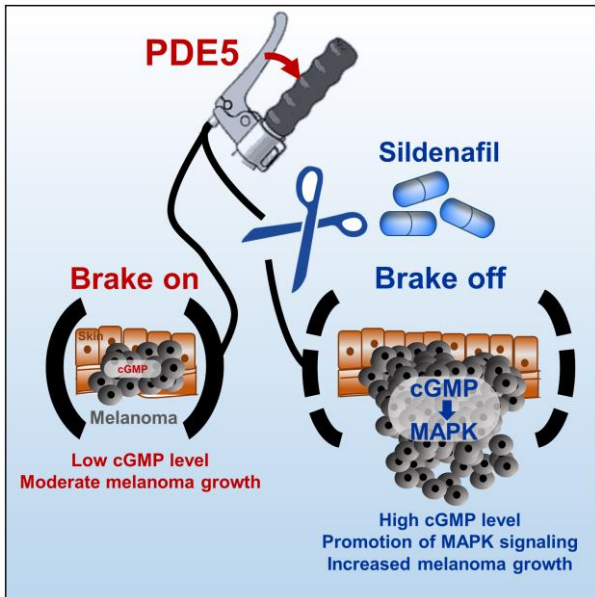
As a signaling molecule, cGMP plays a key role in many complex metabolic pathways, from cells in blood vessels and the heart, to neurons and sensory cells. Its precise effects on both desirable and undesirable growth processes in the body are not well understood. In 2013 the German Research Foundation (DFG) sponsored the research unit, cGMP Signaling in Cell Growth and Survival, at the University of Tübingen.

“We have discovered that the cells of malignant melanoma also use the cGMP signaling pathway for their growth,” says Feil. Normally, cells contain an enzyme – phosphodiesterase type 5 (PDE5) – which ensures that newly-formed cGMP is continuously broken down. Sildenafil, however, inhibits the enzyme. “PDE5 is like a brake on cGMP,” says Feil. “Taking Sildenafil basically disables this brake.” Feil adds that as a result, the melanoma begins to grow more vigorously. This biochemical mechanism may explain why men who take Sildenafil have an increased risk of melanoma.

Researchers have debated a possible link between Sildenafil and cancer for several years. A long-term study of some 15,000 men in the United States published in 2014 suggested that Sildenafil was connected to a higher risk of malignant melanoma. A correlation was confirmed in 2015 by another study of around 24,000 men in Sweden. Yet neither study was able to say whether the increased melanoma risk is in fact due to a biological effect of the drug on tumor cells. They were unable to discount the possibility that a higher incidence of skin cancer in men using Sildenafil may be due to their lifestyles, which included sunbathing holidays and visits to the solarium.

Professor Feil stresses that even given these latest findings, there is no reason for men to refrain from occasionally taking PDE5 inhibitors to treat erectile dysfunction. He says further studies are necessary to gauge the applicability of the findings to humans. And he adds that it is unlikely that the drug leads to new cancers forming. “We are assuming that Sildenafil and possibly other PDE5 inhibitors could first and foremost reinforce the growth of existing melanomas – particularly if these medications are taken frequently and in high dosages,” says Feil.

Findings by other research groups indicate that Sildenafil may have an inhibitive effect on other kinds of tumors – for instance inhibiting the growth of certain intestinal tumors, Feil says. But he adds that melanoma patients should consult their doctors before using it. “Ultimately, we should all be thinking about reducing our risk of skin cancer and cutting our exposure time to the sun, as well as using effective UV protection,” Feil warns.



How Sildenafil affects the growth of melanoma cells: The enzyme phosphodiesterase type 5 (PDE5) breaks down cGMP, functioning as a brake on skin cancer growth. Sildenafil inhibits PDE5, releasing the brake and causing the cGMP level to rise. That means melanomas can grow more vigorously. Graphic: Robert Feil

Publication:

Sandeep Dhayade, Susanne Kaesler, Tobias Sinnberg, Hyazinth Dobrowinski, Stefanie Peters, Ulrike Naumann, He Liu, Robert E. Hunger, Martin Thunemann, Tilo Biedermann, Birgit Schittek, Hans-Uwe Simon, Susanne Feil, and Robert Feil, Sildenafil Potentiates a cGMP-Dependent Pathway to Promote Melanoma Growth. *Cell Reports* (2016), <http://dx.doi.org/10.1016/j.celrep.2016.02.028>

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