Researchers discover a novel double dagger anti-cancer agent

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Alexander Levitzki, pictured in Berlin, Germany, receiving the European Federation of Medicinal Chemistry's prestigious Nauta Award for Pharmacochemistry. Credit: EFMC

Cancer is a highly complex disease in which the tumor recruits its surrounding tissue, as well as the immune system to support and promote its own growth. This realization explains why tumor therapy has been

difficult for physicians. Researchers now realize that not only does the tumor need to be targeted, but also its microenvironment and the immune system, which is subverted by the tumor to support it.

Two studies in the October 2015 print journal, *Ocogene*, focus on new potential drug-treatment research through a careful study of, and link between, colorectal cancer and melanoma.

Long-time cancer researcher Alexander Levitzki, Wolfson Family Professor Emeritus of Biochemistry at the Hebrew University of Jerusalem, and his senior colleagues, Efrat Flashner-Abramson and Dr. Hadas Reuveni, and other colleagues, describe a double-edged molecule known as NT157 and its action against metastatic human melanoma. In an accompanying article in the same journal, Prof. Michael Karin, a highly acclaimed scientist from the University of California, San Diego, in collaboration with Prof. Levitzki's laboratory, shows the dramatic therapeutic effects of NT157 on colon cancer in a mouse model, which faithfully mimics the human disease.

This unique family of compounds inhibits the action of proteins within the tumor itself, the action of these two cancer-driving proteins in the cancer-supportive microenvironment, as well as the action of "pro-tumor" immune cells, according to Prof. Levitzki. These molecules target two different proteins, comprised of a completely different mechanism of action.

A family of small organic molecules, which fulfills these aims, was developed by the Hebrew University's Alexander Silberman Institute of Life Sciences, in collaboration with the oncological pharmaceutical company, TyrNovo, which licensed NT157 from the Yissum Research Development Company of the Hebrew University of Jerusalem. In his five decades of cancer research, Prof. Levitzki has been the recipient of many international awards, including the Wolf Prize for Medicine.

As part of the NT157 research, the mechanism of these molecules was deciphered by Flashner-Abramson as part of her Ph.D. thesis in the Levitzki laboratory, and by Dr. Reuveni, CEO of TyrNovo (and previously NovoTyr Therapeutics Ltd.). These molecules target two different proteins, comprising of a completely different mechanism of action.

This action was highly unexpected and unforeseen.

Dr. Elza Sanchez-Lopez, from UC San Diego Prof. Karin's lab, conclusively shows that due to the dual targeting feature of NT157, both the tumor and conducive microenvironment became suppressed; a highly effective activity against colon cancer.

"The understanding that cancer is a manifestation of signal transduction gone awry has led to the development of 'targeted therapy' or 'signal transduction therapy,' aimed at cancer-driving proteins," according to the paper, formally titled "Targeting melanoma with NT157 by blocking Stat3 and IGF1R signaling."

Signal transducer and activator of transcription 3 (Stat 3) is a protein that has attracted much interest as a target for anti-cancer drugs. Stat 3 is a member of a family of seven latent cytoplasmic proteins (organisms such as bacteria, which lack a cell nucleus) and that function as key mediators of cytokine (small proteins) and growth factor signaling.

In the second paper, titled "Targeting colorectal cancer via its microenvironment by inhibiting IGF-1 receptor-insulin receptor substrate and STAT3 signaling," researchers looked at the tumor microenvironment (TME). TME exerts critical pro-tumorigenic effects through cytokines and growth factors that support cancer cell proliferation, survival, motility (capability of movement), and invasion.

Colorectal cancer (CRC) is the third most commonly diagnosed cancer, with more than 1.2 million cases each year in the United States. While improved early detection and patient stratification (categorization), results in a significant reduction of mortality, most improvement has been limited to early stage CRC. In patients with advanced stages of the disease, morbidity and mortality remain high.

Tumor development is highly dependent on intricate interactions between multiple cell-types, in addition to malignant epithelial (membranous tissue covering internal organs and other internal surfaces of the body) cells that harbor oncogenic mutations. As in the case of melanoma, anti-cancer drugs for CRC are frequently ineffective against cancer-cells that are therapeutic target which concomitantly affect the malignant behavior of cancer cells and the supportive function of the TME is of particular importance.

Therapies that target TME components in addition to cancer cells should have strong anti-tumor activity.

A prospective study of a cohort of 210 CRS patients shows that tumor size and depth of invasion significantly correlate with IGF-1 and IGF-1R, an insulin-like growth deficiency.

Specific signal transduction inhibitors, a category of anti-cancer drugs that inhibit the enzymes essential to the growth and survival of cancer cells while causing little or no damage to non-cancer cells, are rarely effective in treating the disease. In most cases, tumors possess primary drug resistance due to their inherent heterogeneity – one of the underlying reasons that make treatment of cancer difficult. Resistance to drugs is due to genomic instability and acquisition.

"Our results strongly support further clinical evaluation of NT157 and similar compounds in sporadic human CRC," according to the paper's

authors

More information: E Flashner-Abramson et al. Targeting melanoma with NT157 by blocking Stat3 and IGF1R signaling, *Oncogene* (2015). DOI: 10.1038/onc.2015.229

E Sanchez-Lopez et al. Targeting colorectal cancer via its microenvironment by inhibiting IGF-1 receptor-insulin receptor substrate and STAT3 signaling, *Oncogene* (2015). DOI: 10.1038/onc.2015.326

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