Researchers identify genes linked to chemoresistance

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Two genes may contribute to chemotherapy resistance in drugs like 5-fluorouracil, which is used in liver cancer treatment, according to Virginia Commonwealth University Massey Cancer Center researchers.

Liver cancer is a highly aggressive form that has limited therapeutic options. One of the key challenges with cancer treatment is that patients can develop resistance to chemotherapy. Researchers are examining ways to prevent resistance by determining the molecular mechanisms involved with cancer progression, and then developing new generations of chemotherapeutic agents.

In the study, published online in the Early Edition of the Proceedings of the National Academy of Sciences the week of July 13, researchers reported that two genes - astrocyte elevated gene-1, or AEG-1, and late SV40 factor, LSF, contribute to resistance of a commonly used chemotherapeutic drug called 5-fluorouracil, or 5-FU. The team found that over-expression of AEG-1 increased resistance of the liver cells to 5-FU. They observed that a second gene, LSF, is under the control of AEG-1 and mediates a series of molecular pathways involved the resistance to 5-FU.

Previous studies suggest that the expression of AEG-1, is very low in normal cells or tissues such as breast, prostate, liver and brain. However, in cancers of the same organs, expression of AEG-1 is significantly increased. AEG-1 was initially cloned in the laboratory of Paul B. Fisher, Ph.D., director of the VCU Institute of Molecular Medicine.

Earlier this year, the team determined that AEG-1 modulates expression of genes relevant to the progression of liver cancer, including invasion, metastasis, resistance to chemotherapy, the formation of new blood vessels and senescence. They identified that LSF, a transcription factor that regulates gene expression, is increased by AEG-1.

"Since AEG-1 is a key regulator of liver cancer development and progression, understanding how this molecule works will provide profound insights into the mechanism of liver cancer development," said principal investigator Devanand Sarkar, Ph.D., a Harrison Endowed Scholar in Cancer Research at the VCU Massey Cancer Center and assistant professor in the Department of Human and Molecular Genetics in the VCU School of Medicine.

"By understanding these molecular pathways and mechanisms, we may be able to create new drugs to inhibit the expression of AEG-1 or LSF and even develop combination drug therapies to enhance the effectiveness of 5- fluorouracil."

"These findings may have important therapeutic implications. Based on the expression level of AEG-1 or LSF in tumor biopsy samples, a clinician might determine whether a patient would respond to 5-fluorouracil and thus design an effective chemotherapeutic protocol," he said.

Sarkar said that AEG-1 contributes to resistance to not only 5-FU, but also to other chemotherapeutics such as doxorubicin and cisplatin, although the molecular mechanism of resistance to the latter drugs is different from 5-FU. The team is currently conducting studies to further understand the molecular mechanisms by which AEG-1 induces resistance to chemotherapy so that this knowledge might be applied to develop strategies to maximize the efficacy of chemotherapeutics. Additionally, novel combinatorial treatment approaches that incorporate

AEG-1 or LSF inhibition in a standard chemotherapeutic protocol will be evaluated for their efficacy in inhibiting liver cancer in animal models.

Source: Virginia Commonwealth University (news : web)