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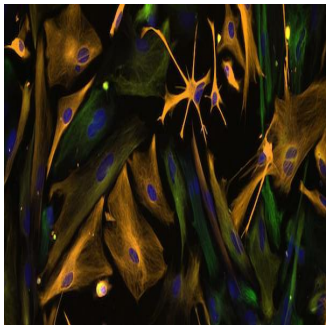
Gene Interaction Discovery Could Lead to New Brain Cancer Therapies



Scientists have identified a new target for future brain cancer therapies, based on a newly discovered interaction between proteins. Researchers at Virginia Commonwealth University (VCU) Massey Cancer Center and the VCU Institute for Molecular Medicine (VIMM) observed that two genes, AEG-1 and Akt2, which are individually present in many types of cancer, participate in a positive feedback loop which promotes the growth and survival of glioblastoma multiforme (GBM), the most common form of brain cancer.

Patients diagnosed with GBM have poor prognoses, which is why the new therapeutic target is significant. In preclinical trials, the researchers were able to reduce GBM cell survival and invasion by disrupting the interaction between AEG-1 and Akt2 through a process called competitive binding. Since expression of these genes correlates with GBM progression — and reduced patient survival — drugs which interrupt the proteins' interaction could be an effective treatment for this type of cancer.

Gene Overexpression in Cancer

The study's lead author, Paul B. Fisher, MPh, PhD, discovered the AEG-1 gene and noticed that it is overexpressed in a majority of cancers. Meanwhile, Akt2 is similarly overexpressed in other types of cancer. Bin Hu, PhD, a senior postdoctoral researcher who works on Fisher's team, is credited with discovering that AEG-1/Akt2 protein interactions spur additional Akt2 signalling. Tumour cells depend on such signalling for basic cellular functions, and can proliferate when the environment is right for binding.

"In this study we mapped the interacting regions in both genes in order to begin the process of developing drugs that can fill in these spaces and block the genes from binding," Fisher said. "If successful, these new treatments could also be applicable to a variety of additional cancers in which both genes are overexpressed."

Disrupting the Signalling Complex

Preclinical trials revealed the effectiveness of competitive binding in disrupting the signalling complex of AEG-1 and Akt2. In mouse models of human GBM, survival increased markedly when AEG-1 was silenced. "If we can develop drugs that disrupt the interaction between these two proteins, we could potentially combine them with conventional therapies to more effectively treat malignant gliomas," said Fisher.

Fisher is the Thelma Newmeyer Corman Endowed Chair in Cancer Research and Director of the VIMM. He also co-leads the Cancer Molecular Genetics research program at VCU Massey, and is a professor and Chair of the Department of Human and Molecular Genetics at the VCU School of Medicine.

The findings of the study have been published online in the journal *Cancer Research*.

Source: Virginia Commonwealth University
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