Small molecules block cancer gene

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Finding molecules that block the activity of the oncogene Stat 3 (signal transducer and activator of transcription) required screening literally millions of compounds, using computers that compared the structure of the cancer-causing gene to those of the small molecules, said a Baylor College of Medicine researcher in a report that appears in the current online issue of the journal *PLoS One* (Public Library of Science ONE).

It was worth the effort, said Dr. David J. Tweardy, professor of medicine and molecular and cellular biology and chief of the division of infectious diseases at BCM, because it could point the way to better treatment of breast and other cancers, as well as chronic viral infections, asthma, and inflammatory bowel disease. He is also on the faculty of Dan L. Duncan Cancer Center.

The "virtual" high throughput screening looked at the possibility of "docking" 920,000 small drug-like compounds into a pocket of a specific domain of Stat3, said Tweardy. In other words, Tweardy and his colleagues identified an area on the Stat3 molecule that was important to its activity. Stat3 actually is critical in keeping malignant cells alive in the majority of cancers.

Once Tweardy and his colleagues had identified a critical "pocket" on Stat3, they used the computer to look for small molecules that would fit in that pocket and block the ability of Stat3 to maintain the cancer cell. That screen of nearly 1 million small molecules identified three likely compounds.

Assays of these compounds showed that they did halt the activity of Stat3 in the laboratory. With that information, Tweardy and his colleagues then screened another 2.47 million compounds for similarity to the original three.

They found another three. While five of the six had some activity in stopping Stat3, one - called 188 - was most effective. Three of the six worked to induce programmed cell death or apoptosis in breast cancer cell lines.

"It induced death in those breast cancer cells that depend for their survival on Stat3," said Tweardy.

Tweardy and his colleagues are now looking at second generation compounds that promise to be even more effective against Stat3.

When he and his colleagues started looking at Stat3, they knew it was important in cancers of the head and neck. Further research showed that it also was important in breast, lung and prostate cancers as well as multiple myeloma (a cancer affect blood-forming cells) and acute myelogenous leukemia.

Stat3 also plays a role in chronic virus infections, asthma, psoriasis and inflammatory bowel disease - all areas that Tweardy and his colleagues hope to pursue in the future.

More information: dx.plos.org/10.1371/journal.pone.0004783

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