Tiny sacs released by brain tumor cells carry information that may guide treatment

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Microvesicles – tiny membrane-covered sacs – released from glioblastoma cells contain molecules that may provide data that can guide treatment of the deadly brain tumor. In their report in the December 2008 *Nature Cell Biology*, which is receiving early online release, Massachusetts General Hospital (MGH) researchers describe finding tumor-associated RNA and proteins in membrane microvesicles called exosomes in blood samples from glioblastoma patients. Detailed analysis of exosome contents identified factors that could facilitate a tumor's growth through delivery of genetic information or proteins, or signify its vulnerability to particular medications.

"Glioblastomas release exosomes in sufficient quantities to pass the blood-brain barrier. We were able to isolate them, analyze the RNA transcripts and show how they might be used as biomarkers to guide targeted therapy and monitor treatment response," says Johan Skog, PhD, the study's lead author, who works in the laboratory of Xandra Breakefield, PhD, at the MGH Neuroscience Center. "Exosomes also may someday be used to deliver therapeutic molecules to the site of a tumor," he added.

Many types of cells release exosomes as part of normal cell-to-cell communication, and several types of tumors are known to shed exosomes containing proteins that can alter the cellular environment to favor tumor growth. The current investigation is believed to be the first to carefully analyze the contents of exosomes shed from glioblastoma cells and characterize their contents.

The investigators first analyzed tumor cells from three glioblastomas and verified that the cells released exosomes containing RNA and protein molecules. Some messenger RNAs related to activities such as cell proliferation and migration, angiogenesis, and immune response were highly abundant in the exosomes. When glioblastoma exosomes were cultured with normal cells, tumor RNA was delivered into the normal cells and generated its encoded protein, supporting the role of exosome-delivered RNA in manipulating the cellular environment.

To study the potential of glioblastoma exosomes as markers of a tumor's genetic makeup, the researchers analyzed tumor tissue and blood serum from 25 glioblastoma patients and were able both to find tumor exosomes and to identify, in some tissue samples, a mutation in the epidermal growth factor receptor (EGFR) gene that characterizes a tumor subtype. In two patients, an EGFR mutation that did not appear in the tumor tissue sample was identified by exosome analysis, reflecting how a surgical biopsy can miss tissue conveying critical information because of the often-chaotic diversity of cells within a tumor.

"It is known that the effects of some anticancer drugs depend on a tumor's genetic mutational profile, so our results have broad implications for personalized medicine," explains Skog, who is an instructor in Neurology at Harvard Medical School. "Detecting mutational profiles through a noninvasive blood test could allow us to monitor how a tumor's genetic makeup changes in response to therapy, which may necessitate changes in treatment strategy." Skog, Breakefield and their colleagues are also investigating the role of exosomes in other solid tumors and how they may help monitor additional tumor-associated mutations.

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study has been exclusively licensed to Exosome Diagnostics, Inc. Subsequent to the completion of this work, Skog was appointed the company's director of Research, while maintaining his position at MGH.

Source: Massachusetts General Hospital