

Lay report:

Tumors require new blood vessels to grow beyond a small, restricted size. To induce the development of blood vessels within the tumor, a process called angiogenesis, cancer cells secrete factors that promote this process as well as down-regulate the factors that inhibit it. This dependence of the tumors on new vasculature offers a very attractive possibility of controlling cancer growth by preventing angiogenesis. We have been intensively studying a protein, Brain Angiogenesis Inhibitor-1 (BAI-1) that may specifically control vessel development in the brain. We have previously shown BAI-1 is absent in a majority of human brain tumors and our plan was to determine if gene promoter methylation causes this loss of BAI-1, as was indicated by preliminary results. Our ongoing experiments have so far confirmed this hypothesis. We have found that a majority of glioblastomas carry methylated DNA at the BAI1 gene promoter. We are now making progress on a detailed physical map of these methylation events in a large set of tumors. Our further plan was to study BAI1 function by generating a knockout mouse lacking BAI-1 expression due to engineered gene deletion. Once we will have these mice we will determine if the loss of BAI-1 reveals any phenotype indicative of its involvement in development. The knockout mice will express a reporter gene when the BAI-1 promoter is activated, which will allow us to establish an expression pattern for BAI-1 expression throughout development. Our progress in this area has been slowed down by unexpected difficulties in generating the plasmid construct that is needed to knockout the BAI1 gene in mice. We have now modified our construction strategy and are at the final step of construction. Once we will have the BAI-1 knockout mice we will be able to cross them with transgenic mice that form spontaneous gliomas to prove that BAI-1 is acting as a tumor suppressor. We expect the tumors in mice lacking BAI-1 to be more angiogenic and aggressive. Our progress in this area has been to acquire the GFAP-Ras transgenic mouse model from Dr Guha at the University of Toronto and start a breeding colony. We have characterized the brain tumor growth pattern of these mice so that we are in a position to compare tumor growth patterns with those we will get in once the cross has been realized. If successful, these studies will support the development of agents mimicking BAI-1 as new therapeutics for GBM, as well as the use of demethylating drugs for reactivation of BAI-1 expression in the brain.