Neuroscience Today, Neurology Tomorrow

Research Reports and Clinical Perspective

Neuroscience Today, Neurology Tomorrow continues its exposition of recent brain tumor–related discoveries. While we continue to emphasize new potential therapeutic pathways, this month's research explores known therapeutic agents that may have a shorter time from the bench to the bedside. We learn about the apparent ability of cyclosporin A to inhibit the pro-invasion effect of microglia on glioma cells both in culture and in mice and the chemotherapy-sensitizing effect that a statin may have on the drug cyclopamine to induce apoptosis in an in vitro study of medulloblastoma cells. Both avenues of research deserve further rounds of study. Please send your comments on this month's column to clinicalneurologynews@elsevier.com.

BY RICHARD J. CASELLI, M.D.

Target Microglia to Stop Glioma

Cyclosporin A in clinically relevant doses can block the interaction between microglia and glioma cells that promotes tumor invasiveness, according to the results of in vitro and in vivo studies in mice.

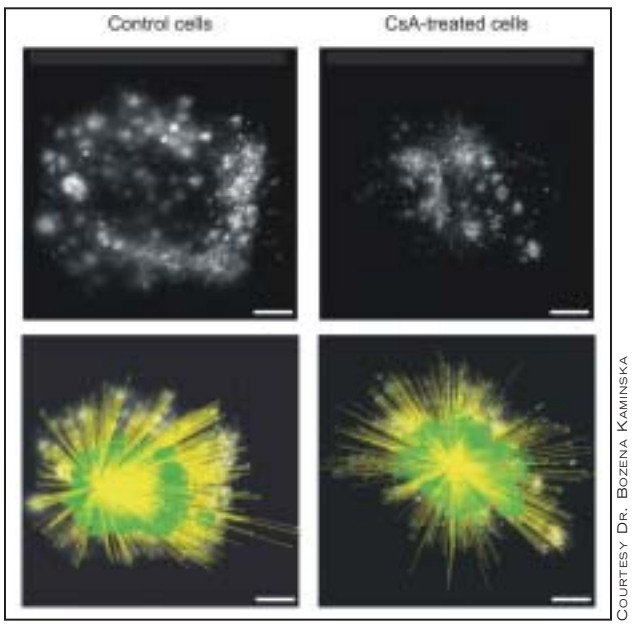
Marcin Sliwa of the Nencki Institute of Experimental Biology, Warsaw, and colleagues discovered that administration of cyclosporin A (CsA) to cultured brain slices that had been inoculated with glioma cells caused significantly fewer tumor cells to spread beyond a radius of 500 mcm after 5 days (33%) than did tumor cells in control slices that were not treated with CsA (77%). There was no difference in the inhibitory effect of CsA at concentrations of 1, 10, and 30 micromol/L (Brain 2007;130:476-89).

In the presence of 1 micromol/L CsA, a significantly higher percentage of glioma cells migrated more than 500 mcm when brain slices were depleted of microglia (67%) than when slices were not depleted (43%). Without CsA, 86% of glioma cells traveled more than 500 mcm in nonmicroglia-depleted slices, whereas 72% migrated that distance in microglia-depleted slices. After CsA treatment, the size of tumors in brain slices that contained microglia declined significantly, but no reduction was seen in microglia-depleted slices.

Fourteen days after gliomas were implanted, the tumors grew to significantly smaller sizes in CsA-treated mice than in control mice (about 0.30 mm^3 vs. 1.23 mm^3). Beginning the second day after implantation, CsA was administered intraperitoneally every 2 days at doses of 2 mg/kg or 10 mg/kg of body weight.

"We hypothesize that blocking unfavorable microglia stimulation with CsA (or similarly acting drugs) will inhibit glioma invasion and in consequence, tumor growth," the investigators reported.

Dr. Caselli's comment: Microglia comprise a significant fraction of the total size of the brain tumor mass, so it should not be surprising that they play an active role in mediating the effects of the tumor. What has been surprising, however, is the relatively recent demonstration that their role is one of promoting rather than inhibiting tumor growth and spread. The lethality of gliomas directly reflects their invasiveness and spread throughout the brain. The demonstration by Dr. Sliwa and colleagues that CsA inhibits glioma growth and spread in both in vitro and in vivo models strongly argues for the drug's advancement to a clinical trial in patients.



Courtesy Dr. Bozena Kaminska

Glioma cell migration from a site of inoculation (bottom) is shown 5 days after treatment with (right) or without cyclosporin A (left); white bar indicates 100 mcm.

Potential Medulloblastoma Tx

Drugs that induce apoptosis in medulloblastoma cells may be effective against more than one subtype of the cancer, according to in vitro studies of human cultures.

In human specimens of medulloblastoma tumors, Eli E. Bar, Ph.D., and his associates at Johns Hopkins University, Baltimore, found evidence to suggest that activation of the Hedgehog (Hh) receptor pathway may promote the survival of medulloblastoma cells by upregulating the expression of BclII, which is an antiapoptotic protein. BclII was found to colocalize with the transcription factors Gli1 and Gli2 in the internodular regions of nodular-subtype medulloblastomas. Gli1 and Gli2 operate in the Hh signaling pathway and are known to bind directly to sequences in the BclII promoter in epithelial cells and induce transcription. Activation of the Hh pathway did not seem to be restricted to the nodular subtype of medulloblastoma because eight of nine tumors (classic, anaplastic, and nodular subtypes) with above-median Gli1 mRNA levels also had above-median BclII levels. In 17 tumors of these different subtypes, elevated expression of Gli1 was significantly correlated with higher expression of BclII; this analysis excluded one quickly metastasizing, diffusely anaplastic tumor that had low Gli1 but high BclII levels that might be accounted for by its increased number of chromosomal abnormalities and other genetic alterations, according to the researchers (Am. J. Pathol. 2007;170:347-55).

In cultures of separate nodular medulloblastoma cell lines, the investigators found that transient and stable transfection of Gli1 clones into these cells led to increases in Gli1 levels, which were associated with significantly higher BclII mRNA expression. In nontransfected cells, blockade of the Hh pathway with cyclopamine significantly reduced the expression of Gli1 after 18 hours and also progressively reduced BclII levels. Medulloblastoma cells that were stably transfected with Gli1 maintained higher Gli1 mRNA levels than nontransfected cells even in the presence of 10 micromol/L of the Hh blocker cyclopamine. The percentage of apoptotic medulloblastoma cells significantly increased after 48 hours of exposure to 5 micromol/L cyclopamine. At that concentration, cells that were transfected with Gli1 clones were able to block apoptotic induction, but only one of the Gli1 clones that expressed higher levels of Gli1 and BclII overcame the effect of 10 micromol/L cyclopamine. The researchers also showed that downregulation of BclII via decreased Gli activity is a major proapoptotic mechanism of cyclopamine.

To see if Hh inhibition with cyclopamine sensitized tumor cells to other proapoptotic stimuli, the investigators administered 5 micromol/L lovastatin and 5 micromol/L cyclopamine to the cell cultures. Lovastatin has been shown to stimulate apoptosis in medulloblastoma. Cotreatment induced apoptosis in 63% of cells, compared with less than 20% in cultures with the same concentration of either agent alone. "This suggests that cyclopamine or other Hh inhibitors might sensitize medulloblastoma to the pro-apoptotic effects of radiation or other chemotherapeutic agents," the researchers noted.

Dr. Caselli's comment: Medulloblastoma is the most common malignant brain tumor in children. Current treatment with radiation and chemotherapy has an impact on the entire developing young brain, so that therapies targeting tumor-specific mechanisms that might spare healthy brain exposure are sought. The sonic hedgehog pathway is known to play an important role in medulloblastoma formation, and Dr. Bar and colleagues have now elucidated the specific mechanism through which this occurs. They further show how therapies targeting this pathway may effectively kill medulloblastoma cells. Cyclopamine, like other chemotherapeutic agents, can cause birth defects (cyclopia), but has been used topically as an experimental therapy for psoriasis. As a sensitizing agent, it may be useful in developing more selective therapies for medulloblastoma, but in vivo models are needed, especially before trials in young children are considered. ■

Clinical perspective by Dr. Caselli, *chair of neurology at the Mayo Clinic, Scottsdale, Ariz., and professor of neurology at the Mayo Medical School, Rochester, Minn.*

Research reports by Jeff Evans, senior writer.

No Link Between Mobile Phone Use and Gliomas, Study Finds

BY JONATHAN GARDNER
London Bureau

Long-term or heavy use of mobile phones does not increase the risk of developing one type of brain tumor, although exclusive long-term use on one side of the head appears to increase the risk slightly.

The case-control study examined mobile phone use among 1,521 glioma patients and 3,301 controls in Denmark, England, Finland, Norway, and Sweden. Mobile phones emit radio waves that some believe play a role in tumor development, although a carcinogenic link has not been established, wrote Anna Lahkola of the Finnish Radiation and Nuclear Safety Authority, Helsinki (Int. J. Cancer 2007 Jan. 17 [Epub doi:10.1002/ijc.22503]).

Researchers conducted interviews with all study participants to identify patterns of mobile phone use among glioma patients and controls. Of the cases, 58% said they had used a mobile phone regularly—at least once weekly for at least 6 months—in the year before diagnosis. A total of 59% of controls reported regular use. Regular mobile phone users had a lower risk of developing gliomas, compared with those who never or seldom used mobile phones (odds ratio 0.78).

Mobile customers who used the phone only on the same side of the head as the location of their tumor had a significantly increased risk of glioma if they started using the phone at least 10 years ago (OR 1.39).

Even among heavy and long-term users, the researchers found no link. "The most exposed group (the highest 10% based on the exposure distribution among controls) did not show an elevated risk of glioma," they wrote. "Neither did the dose-response analyses reveal a clear trend in relation to the overall duration of mobile phone use, number of calls, or hours of use." The authors acknowledge that "selection bias may have produced an apparent protective effect of mobile phone use." ■