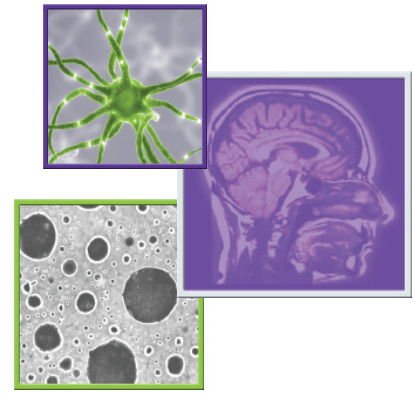
Controlled fasting could aid radiation therapy for glioma sufferers



"You want to balance the risks. You have to do it right. But if the conditions are such that you've run out of options, short-term fasting may represent an important possibility for patients."

Controlled fasting during radiation therapy could be a new strategy for the treatment of gliomas, the most commonly diagnosed brain tumor. Researchers at the University of Southern California (CA, USA) hope that this technique will greatly improve life expectancy for sufferers.

The study, recently published in *PLoS ONE*, shows that twice as many infected mice survived when they experienced a combination of radiation therapy and controlled fasting compared with radiation therapy or controlled fasting alone. The study had foundations in prior work in which the team had discovered that short-term fasting projects can help to save the healthy cells in the body while cancerous cells are left vulnerable to radiation therapy. This information was then applied to the treatment of gliomas: "with our initial research on chemotherapy, we looked at how to protect patients against toxicity. With this research on radiation, we're asking what are the conditions that make cancer most susceptible to treatment? How can we replicate the conditions that are least hospitable to cancer?" commented Valter Longo (University of Southern California) a corresponding author on the study.

Research focused on radiation therapy delivered after the surgical removal of a brain tumor. It featured the use of temozolomide, which is commonly given in these circumstances. The mice were subjected to fasting periods that each lasted no more then 48 h. At the end of the trial period, the combination of successive fasting periods with radiation therapy was shown to be very successful.

In the future, the researchers feel this controlled fasting technique could be applied to humans. However, Longo feels caution must be applied to all those wishing to try it themselves: "You want to balance the risks. You have to do it right. But if the conditions are such that you've run out of options, short-term fasting may represent an important possibility for patients."

– Written by Natasha Galukande

Sources: Safdie F, Brandhorst S, Wei M *et al.* Fasting enhances the response of glioma to chemo- and radiotherapy. *PLoS ONE* 7(9), e44603 (2012); Fasting makes brain tumors more vulnerable to radiation therapy: www.sciencedaily.com/releases/2012/09/120911172308.htm

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Alternative nanoparticle covering shows great promise

Researchers at the Johns Hopkins University School of Medicine (MD, USA) have designed a nanoparticle drug-delivery system that is reported to be more effective than any others that have previously been seen. The study, recently published in *Science Translational Medicine,* could aid in delivering chemotherapy to hard-to-reach areas of the brain following surgery.

Delivering chemotherapy to the brain is fraught with many problems, such as difficulties in supplying a large enough dose and reaching targeted brain tissues. However, the newly designed nanoparticles are able to safely deliver a larger quantity of drugs for a longer time period to more complex areas.

Nanoparticles hold drug molecules in a tightly bound structure that is loosened, and the drug molecules released, when water is present; however, there are several problems that must be overcome to improve its efficiency. The success of this new nanoparticle, tested in *in vivo* rodents and *in vitro* human tissue, is largely attributed to it overcoming the previously encountered problem of sticking to its surroundings, preventing it from reaching its target.

"We are pleased to have found a way to prevent drug-embedded particles from sticking to their surroundings so that they can spread once they are in the brain," commented Justin Hanes, director of the Johns Hopkins Center for Nanomedicine.

The study involved several stages. Initially, nano-sized plastic beads ranging in size were coated with the molecule poly(ethyl)ene glycol (PEG), before being injected into slices of rodent and human brain tissue. The team was able to watch the beads as they made their way through the brain tissue because the beads were labeled with glowing tags. It was discovered that the level of PEG coating on the beads correlated with their ability to penetrate the brain tissue in both rodent and human brain slices. Densely coated PEG beads double the size of what the team had previously thought was possible were able to penetrate rodent and human brain slices. The next stage of the experiment involved testing the same beads in *in vivo* rodents, which gave equally promising results. Finally, the team of researchers applied PEG to biodegradeable nanoparticles carrying the commonly used chemotherapy drug paciltaxel, with the results obtained following the previous positive trend. Nanoparticles with a greater PEG covering were more efficient at delivering drugs than those that had less PEG covering.

"It's really exciting that we now have particles that can carry five-times more drug, release it for three-times as long and penetrate further into the brain than before," commented Elizabeth Nance (Johns Hopkins University School of Medicine).

The team plan to continue their experiments on rodents to establish the effect that using PEG-covered nanoparticles will have on preventing tumors, "the next step is to see if we can slow tumor growth or recurrence in rodents," commented Graeme Woodworth, neurosurgeon at John Hopkins. The team also plans to explore its efficiency in delivering drugs for the treatment of other diseases of the brain, such as multiple sclerosis, stroke, traumatic brain injury, Alzheimer's and Parkinson's.

– Written by Natasha Galukande

Sources: Nance EA, Woodworth GF, Sailor KA *et al.* A dense poly(ethylene gycol) coating improves penetration of large polymeric nanoparticles within brain tissue. *Sci. Transl. Med.* 4(149), 149ra119 (2012); Improved nanoparticles deliver drugs into brain: www.sciencedaily.com/releases/2012/09/120911151833.htm

Searching for genomic alterations that increase the risk of brain tumors

Complex genomic techniques employed by researchers at the Mayo Clinic (MN, USA) and University of Southern California (CA, USA) have revealed important information that could help to identify people at risk of specific brain tumors.

The study, recently published in *Nature Genetics*, describes how having a G, instead of an A, on a spot of the genetic code confers a sixfold higher likelihood of the subject developing specific kinds of brain tumor. While the researchers are not sure if they have identified the specific spot on the genome that affects this, they are certain that they are close.

The results are the culmination of several years of research by the teams into regions on the genome that are involved in an increased risk of gliomas. A proportion of chromosome 8 was identified to contain several single-nucleotide polymorphisms associated with brain tumors. From there, the team worked to identify the single-nucleotide polymorphism that caused an increase in gliomas, identifying seven promising candidates; one of which has since been associated with an increased likelihood of slower-growing gliomas.

– Written by Natasha Galukande

Sources: Jenkins RB, Xiao Y, Sicotte H *et al.* A low-frequency variant at 8q24.21 is strongly associated with risk of oligodendroglial tumors and astrocytomas with *IDH1* or *IDH2* mutation. *Nat. Gen.* 44(10), 1122–1125 (2012); Genomic variant discovered that increases risk of brain tumors: www.medicalnewstoday.com/releases/249495.php

"...the team worked to identify the single nucleotide polymorphism that caused an increase in gliomas, identifying seven promising candidates."

Virtual reality simulator designed to improve brain cancer surgeon skills

A new surgery simulator to help surgeons develop their brain cancer surgery skills has been developed by the National Research Council Canada (ON, Canada). Surgery simulators have been devised previously, but the team, led by Sébastien Delorme, has designed a system that includes several new features, including tactile feedback and 3D graphics for the user. The development of the system, named NeuroTouch, is described in the journal *Neurosurgery*. It incorporated feedback from more than 50 experts from the National Research Council Canada.

The training tasks developed for the system were constructed from magnetic resonance images taken of brain tumor patients. There are two training operations run on the simulator, a tumor debulking and a tumor cauterization task, incorporating three surgical skills.

In the debulking task, the surgeon is challenged with complete tumor removal while retaining normal healthy tissue using a regular surgical aspirator (suction) and the ultrasonic aspirator. In the cauterization tasks, the surgeon uses an aspirator to remove a vascularized tumor, controlling blood loss using bipolar electrocautery.

Delorme described the next steps in the development of the NeuroTouch system, "First-generation NeuroTouch prototypes

"First-generation NeuroTouch prototypes have been set up in seven teaching hospitals across Canada, to be used for beta-testing and validation and evaluated for integration in a neurosurgery training curriculum."

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– Written by Sean Fitzpatrick

Sources: Delorme S, Laroche D, Diraddo R, Del Maestro RF. NeuroTouch: a physics-based virtual simulator for cranial microneurosurgery training. *Neurosurgery* 71(Suppl. 1), 32–42 (2012); Wolters Kluwer Health: www.wolterskluwer.com/press/latest-news/2012/pages/pr20Sep2012.aspx

Exploring the attraction of metastatic cancer cells to the brain

Researchers working in Tel Aviv University's Department of Cell Research and Immunology (Israel) have begun exploring the factors influencing the attraction of metastatic melanoma cells to the brain. By uncovering how these cancer cells are able to travel from a primary tumor site and cause a secondary tumor in the brain, it is hoped that more effective targeted therapy for melanoma brain metastasis can be developed.

In their work, which was published in the *International Journal of Cancer*, the team focused on the working hypothesis that specific interactions that occur between the brain microenvironment and melanoma cells cause the metastasis. They explored this by assessing the formation of brain metastasis in nude mice that had been xenografted with human melanoma cells. Once metastatic melanoma cells have become established in the brain, the survival prognosis for sufferers is only a few months.

It was discovered that the melanoma cells are able to produce receptors for two chemokines that are present in brain tissue. These receptors could potentially cause the attraction of cancerous cells to the brain, acting as a so-called 'homing device'. It is this information that could be useful in future studies "These interactions between the chemokines in the brain and the melanoma cell receptors could be potential targets for new therapies. With medications that suppress these molecules, you could hope to interfere with this specific migration," commented Isaac Witz (Tel Aviv University), a researcher of the study.

The two chemokines were identified when analyzing all the materials that were expressed by cells present in the cultured brain tissue. The team noticed that specific chemokine receptors in brain-metastasizing melanoma cells have corresponding chemokines in the brain tissue. Therefore, if a chemokine is released from a certain point, the melanoma cells with the correct receptors will be attracted to this spot.

The team also studied the differences between metastatic and nonmetastatic cells that have the same genetic background to determine which genes are specific to metastatic cells and therefore what causes cells to become metastatic. It was discovered that mice that had received nonmetastatic cells still have melanoma cells in their brain but these are dormant. Therefore, this information paves the way for future exploration into how cancer cells that have spread to different places then divide and propagate.

It is hoped that by exploring the differences in metastatic and non-metastatic cells future researchers will be able to, "duplicate what nature does, and prevent these cells from becoming metastatic. If there already is metastasis, it is too late – so what we want to do is to prevent development by understanding the mechanism that keeps the nonmetastatic cells dormant."

– Written by Natasha Galukande

Sources: Klein A, Sagi-Assif O, Izraely S *et al.* The metastatic microenvironment: brain-derived soluble factors alter the malignant phenotype of cutaneous and brain-metastasizing melanoma cells. *Int. J. Cancer* 131(11), 2509–2518 (2012); Fighting melanoma's attraction to the brain: www.sciencedaily.com/releases/2012/09/120919125602.htm