The Immune System and Degenerative Brain Disorders

Emerging evidence suggests that the immune system plays an early role in protecting against neurodegenerative disorders of the central nervous system.

Michal Schwartz, PhD

Most research related to the immune system in general has aimed at identifying its various components, describing their actions and interactions, and investigating their roles in detecting and defending against pathogens. Only lately has it been recognized that the immune system also has a role in tissue maintenance. In the context of the brain, it was commonly believed that under normal conditions, the central nervous system (CNS) functions best without interference from immune cells, but according to our studies, autoimmune T cells are always needed for maintaining the functional integrity of the CNS through elaborate mechanisms that are yet to be fully described.

My colleagues and I were among the first to recognize that innate immune cells (macrophages/microglia) play an essential part in CNS recovery, as opposed to the prevailing belief that these cells only add to the chaos. We found that spontaneously recruited macrophages following injury have a crucial and beneficial role in CNS repair (site, timing, dosing and activity are critical) that cannot be replaced by the resident CNS immune cells, the microglia. We proposed a paradigm shift in the perception of autoimmunity in the context of the CNS, attributing to autoimmune T cells (partly via recruitment of blood-borne monocytes) a key role in CNS plasticity in health and disease: maintenance, protection and renewal from adult stem cells. We formulated the concept of “protective autoimmunity”, which is now widely used to distinguish between autoimmunity as the body’s mechanism of maintenance and defense, and autoimmune disease, an outcome of an uncontrolled autoimmune response to threats.

Our experience suggests that in addition to its host defense activities, the immune system provides constant maintenance and surveillance of the tissues of the CNS, even under normal, disease-free conditions. It detects and responds to subtle, early changes in homeostasis, including those resulting from neurodegenerative processes and disorders. When tissue integrity is compromised, a properly functioning immune system answers with a silent sequence of increasing levels of corrective actions. If these attempts to maintain the integrity and plasticity of CNS tissues fail, brain dysfunction results or a dormant neurodegenerative disease emerges. According to our hypothesis, a variety of disorders may stem from the immune system’s inability to meet the need for maintenance when CNS tissues are repeatedly injured or inundated by an accumulation of disease risk factors. When accumulated assaults overwhelm the immune system’s ability to provide daily maintenance and repair, disease erupts, but by the time symptoms appear the disease process is already well-established and resistant to treatment.

We are currently studying the possibility that a malfunction of self-specific immune activity interrupts the immune system’s ability to properly maintain CNS tissues, and that this malfunction may explain onset and/or progression of diseases such as Alzheimer’s disease and dementia – and disorders that result in abnormal brain activity – such as psychiatric illnesses. In addition, Cedars-Sinai researchers are currently developing immune-based therapies for treating Alzheimer’s disease, spinal cord injury and ALS. Such treatments are likely to arrest degeneration and promote renewal and repair.

We also are identifying mechanisms and processes by which neurodegenerative disorders escape immune surveillance. When the immune system initially encounters a deviation from homeostasis Continued on page 2 (see “Immune System”)
New Tactics in the War against Brain Tumors

John S. Yu, MD

Attempts to treat malignant brain tumors through the traditional approaches of surgery, radiation and chemotherapy have seen very limited success. With their poorly defined borders, rapid infiltration of normal brain, and migratory characteristics, gliomas defy straightforward treatment options, which must be used with caution and restraint because of their destructive potential.

New approaches promise to undermine malignant brain tumors through mechanisms at the molecular and cellular levels, dismantling cancers from the inside without injury to normal adjacent cells. Stem-cell interventions, genetic manipulations and immune system activation are among the new generation of therapies that may be used individually or in combination to target specifically brain cancer cells.

Brain tumor stem cells

Researchers within Cedars-Sinai’s Department of Neurosurgery are studying the molecular mechanisms underlying brain tumor stem cells (BTSCs), which we isolated from malignant brain tumors in 2004. These self-renewing cells are responsible for brain tumor initiation and propagation. Developing gene expression profiles of these cancer stem cells gives us an opportunity to generate unique molecular signatures of glioblastomas and identify key mechanisms that may predict prognosis and guide treatment decisions.

In recent gene expression studies of BTSCs, we focused on the role of the sonic hedgehog (SHH) signaling pathway, a mechanism that is important in regulating both normal stem cell growth and cancer stem cell growth. Among other findings presented at the International Society for Stem Cell Research earlier this year, we identified both hedgehog-dependent and hedgehog-independent brain tumor stem cells and found that a subset of glioblastomas with the SHH signaling pathway turned on are associated with reduced patient survival times.

Further investigation of SHH and other pathways may allow us to devise new techniques to treat malignant brain tumors with genes or small molecules that attack mechanisms in the stem cells that allow the cancers to exist and grow.

Tumor immunotherapy

We also are conducting preliminary studies to target brain cancer stem cells immunologically. We recently identified a protein that is highly expressed in glioblastoma stem cells but is absent in neuronal cells, raising the possibility that this protein could serve as a target for cytotoxic T cells.

Our Phase II trial of dendritic cell immunotherapy against malignant brain tumors (IRB #3368) recently yielded data that we believe will help guide and evaluate future vaccine-related research. The study was the first to show direct and continual proportionality between the strength of anti-tumor responses and clinical benefits in cancer patients. This demonstration that the magnitude of immune response is directly related to survival gives us a very good “surrogate marker” for clinical benefit. If we can improve the immune response to our vaccine, we can anticipate that the clinical benefit will be improved as well.

The study, published in the July 15 issue of Cancer Research, provided the first known documentation of a definite immune response/patient outcome correlation that can be credited to tumor-altering therapeutic interventions. It also confirmed our earlier finding that dendritic cell vaccination and chemotherapy work synergistically to improve treatment. Time-to-tumor progression increased significantly when vaccination was followed by chemotherapy, compared to vaccination alone.

Reovirus therapy

Because many gliomas have a defect in the Ras signaling pathway, we are participating in a multicenter trial of a reovirus that exploits this vulnerability to infect and kill cancer cells (IRB #13574). Although not every cell line has an activated Ras pathway, Ras activation is very common in gliomas, and the reovirus appears to be effective in killing tumor cells without affecting normal cells.

Like other therapies aimed at the molecular structure of cancers, reovirus therapy may be an especially appealing option for certain patients who are not good candidates for surgery because their cancer is too widespread or in an eloquent area of the brain. After a biopsy of the tumor, the cancer-killing virus is implanted directly into the tumor.

Brain tumors, like all cancers, are complex, highly diverse entities, and we cannot anticipate the development of a one-size-fits-all treatment or cure. Instead, therapies will be combined and specially designed to target each cancer’s unique makeup and vulnerabilities. Therefore, research continues to chip away at the building blocks of cancers from a variety of angles to destroy tumors and leave healthy brain cells intact.

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in the CNS, it attempts to limit the injury and repair damage. If unable to stop the threat and regain balance in this elimination phase, it continues to fight in the equilibrium phase, postponing the onset of symptoms but failing to halt the disease process. Eventually, through suppression of the immune response or the existence of an out-of-control local inflammatory response, the disease escapes surveillance, and symptoms appear.

Because local inflammation is common in neurodegenerative diseases, most treatment approaches have included the use of anti-inflammatory drugs. Although this appears helpful in some animal studies, it may have little benefit or even negative consequences for some patients. It is our contention that blocking inflammation with the drugs that are available today may be counterproductive because it denies the potential beneficial role of peripheral immunity in restoring homeostasis and controlling the local inflammation.

In our view, the immune system is quietly at work in the very earliest stages of the development of neurodegenerative disorders and other CNS conditions. This leads to the possibility that therapies boosting the immune system – particularly during the critical equilibrium stage – could enable it to thwart these devastating illnesses even before the onset of symptoms.
Gene Therapy Strategy to Engineer Brain Tumor Immune Microenvironment Elicits Tumor Regression

Maria Castro, PhD and Pedro Lowenstein, MD, PhD

A new gene therapy approach that attracts and “trains” immune system cells to destroy deadly brain cancer cells also provides long-term immunity, produces no significant adverse effects and – in the process of destroying the tumor – promotes the return of normal brain function and behavioral skills.

This study was conducted in a recently developed laboratory rat model of glioblastoma multiforme (GBM) that closely simulates outcomes in humans and supports the translation of this procedure to human clinical trials early next year. Results of the study were published in Molecular Therapy.

Glioblastoma multiforme, the most common and deadly type of primary brain cancer, usually claims the lives of 90 percent of patients within 24 months of diagnosis. It is extremely difficult to treat for a variety of reasons. GBM tumors grow rapidly, often becoming large before a diagnosis is made. Also, cells readily infiltrate neighboring brain tissue, hampering complete surgical removal. Chemotherapy and radiation therapy are useful adjuvants, but sadly remain unable to eliminate all residual GBM cells, which frequently become resistant to the treatments.

The blood-brain barrier also prevents chemotherapy from effectively reaching tumor cells, and key cells needed to launch and sustain a therapy from effectively reaching tumor cells, – dendritic cells or antigen-presenting cells – do not naturally occur within the brain.

The research team used a gene therapy approach to sidestep these challenges, using a virus stripped of its disease-causing genes as a vehicle to deliver two therapeutic proteins directly into the tumor cells. One protein, FMS-like tyrosine kinase 3 ligand (Flt3L), drew dendritic cells into the brain. Another protein, herpes simplex virus type 1 thimidine kinase (HSV1-TK), combined with the antiviral ganciclovir (GCV), killed tumor cells. Dendritic cells clean up debris from dying cells and in the process alert immune system cells of the existence of foreign glioma antigens. Newly “educated” immune system cells then swarm to the tumor cells to destroy them.

Humans with GBM often suffer behavioral abnormalities that affect concentration, memory and balance. In the animal studies, tumors induced abnormal behavior. The research team found that as the tumors grew, they displaced and compressed nerve terminals and impulse-conducting axons. But long-term survivors who had received the gene therapy did not have long-term injury or behavioral impairment resulting from the tumor or the treatment. Gene therapy eliminated the tumor mass and reversed the deficits that were caused by the tumor.

In an earlier study, the research team used HSV1-TK and GCV alone to treat GBM and found that about 20 percent of the animals survived. By adding the dendritic-cell inducing Flt3L, the survival rate jumped to about 70 percent. Systemic immune activity was sustained, even fending off a “re-challenge” with additional tumor cells. In this study, the researchers reported that this therapy could also revert behavioral abnormalities caused by the growing tumor in the brain.

These findings constitute a significant milestone in creating an effective treatment for GBM. This therapy significantly improved survival rate, induced long-lasting systemic anti-tumor immunity, and resolved the neuropsychopathological abnormalities caused by the tumors, which has been a stumbling block to many promising treatments.

Dr. Castro is Co-Director and Dr. Lowenstein is Director of the Cedars-Sinai Board of Governors Gene Therapeutics Research Institute. Both are principal investigators of the study.
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Case Study: Extreme Lateral Interbody Fusion

Burak M. Ozgur, MD

Many complex disorders and debilitating injuries of the spine that once required large incisions and long months of inactivity and recovery can now be corrected with minimally invasive techniques that spare muscle, drastically reduce blood loss and the need for transfusions, and allow patients to go home in days with minimal discomfort and lifestyle disruption.

In certain cases, several techniques may be used in combination to access different levels of the spine and to accomplish a variety of objectives. Among the more common combinations today is the lateral approach to lumbar disc fusion with minimally invasive positioning of pedicle screws for stabilization.

Using the extreme lateral interbody fusion (XLIF) technique, we now access the spine of the low back (T10-L5) from the side, which provides a safe corridor that does not include the risk of abdominal complications that exists with the anterior approach. The XLIF procedure, performed under fluoroscopic imaging and electrophysiologic monitoring, can be used to treat spondylolisthesis, recurrent disc herniations, foraminal stenosis, degenerative disc disease, degenerative scoliosis and pseudoarthrosis.

This procedure was an ideal choice for a 40-year-old patient who had been involved in a car accident five years before she called my office to schedule an evaluation. The injury had caused serious degeneration of the two discs between L3 and L5, and she underwent lumbar laminectomy at the time. Fusion was discussed, but she wanted to wait until technology provided a minimally invasive option for multiple-level disc repair.

The patient had led a very active and athletic life, but severe pain after the accident restricted her activity and even her ability to drive. She was unable to achieve long-term pain relief even with selective nerve root blocks and other measures.

In her XLIF procedure, we removed the discs and replaced them with polyetheretherketone (PEEK) cages containing bone and bone morphogenetic protein (BMP) to enhance fusion. We then performed a percutaneous lumbar spine fixation, inserting rods and screws through small incisions, using guide tubes and X-ray fluoroscopy for navigation.

All incisions were closed with resorbable stitches on the inside and glue on the skin to provide a good cosmetic result. Small dressings were placed on the wounds.

The patient was discharged from the hospital three days later. An out-of-state resident, she stayed locally with family for about a week before returning home. She was able to reduce her pain medication quickly to only Tylenol, and was eager to return to her previous activities. I saw her recently at six-month follow-up and she is doing very well.

Whether spinal fusion is performed traditionally or minimally invasively, the results are the same in terms of instrumentation and stability. Surgeons are always concerned that spinal fusion will lead to destabilization of adjacent levels over time, and in this respect, I believe the minimally invasive approach may actually lower risk through reduced trauma to muscle, ligaments and structures.

Patients undergoing minimally invasive spine surgery are sidelined for only a short time and bear few scars, but radiographic evidence suggests that even complex spine procedures are now being accomplished under the surface without many of the risks and restrictions of major open surgery.

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