Cancer Therapy – Opioid growth factors

A Unique Biotherapeautic Agent

ENDORPHINS

Endorphins were discovered in 1975 by Dr. John Hughes and Dr. Hans Kosterlitz.

The word Endorphin is abbreviated from 'endogenous morphine' this means a morphine-like substance produced naturally in the body.

The body produces a number of endorphins, which have numerous functions in the body. These range from control of pain and mood to regulation of the immune system, growth of cells and angiogenesis.

OGF

One of these endorphins, met-enkephalin, has been studied extensively in relationship to growth – especially cancer. OGF (Opioid Growth Factor) is a name which has been given to met-enkephalin, in order to symbolize and emphasize its action in relation to control of growth of cells.

Professor Ian S. Zagon and a research team, at The Pennsylvania State University, the M.S. Hershey Medical Center, discovered that endogenous opioid peptides served as growth factors. In subsequent studies, these researchers found that one native opioid peptide – met-enkephalin (OGF) regulates the growth of cancer cells. They further discovered that the effect of OGF is mediated by a receptor. Originally named the (zeta) receptor because it was thought to be a new member of the opioid receptor family, recent cloning and sequencing of this receptor has demonstrated that it is not like classical opioid receptors. The receptor for OGF was renamed the Opioid Growth Factor receptor (OGFr). Of the wide variety of cancer cells examined to date, all use the OGF-OGFr system in growth regulation.

The effect of OGF is to delay the replication of cells. The retarding of cell multiplication is often referred to as cytostatic (cyto = cellular growth, static = halt). Unlike chemotherapy, OGF does not directly destroy cancer cells and is not cytotoxic.

It does however halt the growth of the cells and is thought to allow immunological mechanisms (e.g. macrophages, natural killer cells) to accomplish the task of destroying the cancerous cells.

OGF also appears to work in harmony with chemotherapeutic agents. When given in combination with OGF, chemotherapy is likely to work in a more efficacious manner.

OGF and Angiogenesis

Angiogenesis refers to the creation of new blood vessels. The pioneer in this field, Professor Judah Folkman of Harvard Medical School, discovered that tumors produce new blood vessels in order to enable them to obtain the nutrients which they need to grow at a rapid pace. This process is known as angiogenesis and this enables tumors to metastasize (spread) to other organs in the body.

Since this discovery, billions of dollars have been invested in developing drugs which can halt this process, thus slowing the growth of tumors or starving them of the nutrient supply which they need.

OGF has been found to inhibit angiogenesis, thus adding to its role in cancer therapy, by inhibition of tumor growth and perhaps metastasis.

Immuno-Regulating Properties

In addition to its anti-cancer effects, OGF has been found to have immunostimulating and immuno-regulating effects. It has been used to treat several autoimmune conditions in human subjects, including Multiple Sclerosis, Uveitis, Behcet's Syndrome, and Optic Neuritis.

It has also been reportedly used to treat AIDS with very good results. Much of this research has been carried out in the USA, Belgium, Croatia and Germany.

Raising NK (Natural Killer) Cell levels

NK cells are part of the ' T ' cell family in the lymphocytes. NK cells focus on destroying virally infected cells and cancer, but also kill bacteria, parasites and fungi.

They are unique in that they have a special ability of recognizing invaders. They specialize in killing virus and cancer cells those other parts of the immune system no longer recognize, for whatever reason.

Any cell that is 'hiding' is vulnerable to attack by NK cells. This is routine occurrence as virus and cancer cells tend to try to 'hide'. When other parts of the immune system are so overwhelmed so as to slow or stop their function, NK cells are the last defense that exists.

Boosting NK cell levels is essential in helping to beat cancer. Studies have demonstrated that OGF significantly raises NK (Natural Killer) cell levels, although the mechanism by which this happens has not yet been fully clarified.

Cancers can be treated with OGF

All the studies which have been carried out to date have consistently demonstrated the existence of OGF receptors in every type of malignancy this has been examined. Furthermore, there have been numerous anecdotal reports of a variety of cancers which respond to an OGF-boosting drug. Studies in animals have clearly determined that the mechanism for this response is through OGF/OGFr interaction. It is therefore reasonable to assume that the responses to this OGF-increasing drug which have been anecdotally reported in humans are similarly mediated via OGF receptors.

The following cancers have either been shown to have OGF receptors and/or have been anecdotally reported to respond to OGF and/or OGF-boosting mechanisms.

Breast Cancer
Cervical Cancer
Colon and Rectal Cancer
Gastric Cancer
Glioblastoma
Head and Neck
Kaposi's sarcoma
Leukemia – Lymphocytic
Liver Cancer
Lymphoma – B Cell and T Cell
Malignant Melanoma
Neuroblastoma
Ovarian Cancer
Pancreatic Cancer
Prostate Cancer
Renal Cell Carcinoma
Small Cell and Non-Small Cell Lung Cancer
Throat Cancer
Tongue Cancer
Uterine Cancer

Pancreatic Cancer

Cancer of the pancreas, a gland in the abdomen that makes insulin and other hormones, is the fourth leading cause of cancer death. Because pancreatic cancer is usually diagnosed after it has spread to other areas of the body, as many as 98 percent of people who are diagnosed with pancreatic cancer will die from it, and only 4 percent will live more than five years.

A booster dose of a substance already found in the body appears to be safe and non-toxic for the treatment of pancreatic cancer, and shows signs of arresting pancreatic cancer cell growth in patients, Penn State College of Medicine researchers report.

" Our previous laboratory and animal studies showed that opioid growth factor, called OGF, can markedly slow down the proliferation of pancreatic cancer cells," said Ian S. Zagon, Ph.D., professor of neural and behavioral sciences, Penn State College of Medicine. "Now, in this first study of OGF in people, we've shown that administering it to supplement the body's own supply is not toxic and may help patients with this almost invariably fatal disease."

In laboratory studies, Zagon and his team discovered that OGF, which is involved in suppression of pain in the nervous system, also controls the production of some cells, both healthy and abnormal. Pancreatic cancer cells have OGF receptors that, when bound with OGF, inhibit additional cancer cell growth. Because cancer cells reproduce so quickly, the body cannot produce enough OGF to bind all of the receptors, so cancer cell growth continues unimpeded.

Zagon's laboratory work suggested that providing enough OGF in the body could bind the OGF receptors, inhibit cancer cell proliferation, and give the body's own defenses time to battle the disease.

For the Phase I clinical study, sponsored by the National Institutes of Health, Zagon's collaborator Jill Smith, M.D., professor of medicine, Penn State College of Medicine, enrolled 21 patients with advanced, inoperable, pancreatic cancer. In one group, OGF was administered intravenously in a saline solution over 30 minutes once per week.

Investigators tested seven different doses ranging from 25 micrograms/kilogram (ug/kg) to 250 ug/kg. Other patients enrolled in the study were taught to self-administer 50 ug/kg doses of OGF twice per day via injection.

Before, during and after intravenous infusion and the initial injected doses, vital signs were monitored and laboratory values were recorded.

The study protocol was approved by the Institutional Review Board at Penn State Milton S. Hershey Medical Center under federal regulations and was conducted in the National Institutes of Health-funded Penn State General Clinical Research Center.

The investigators found that the maximum tolerated dose of OGF administered intravenously was 250 ug/kg. At 250 ug/kg, two patients experienced mild symptoms of toxicity, the most severe of which was temporary hypotension, or low blood pressure.

In a second part of the study, 10 patients were treated with 250 ug/kg intravenous infusions of OGF, this time delivered over 45 minutes. Because the timing of drug delivery was extended, there were no incidents of toxicity. Six other patients were treated with 50 ug/kg OGF injections twice per day.

Results showed that, unlike the chemotherapeutic agents often used to treat pancreatic cancer, OGF did not cause white blood cell, platelet or iron counts to drop, and did not cause gastrointestinal problems. Nor were there side effects such as hair loss, nausea or loss of appetite.

Quality of life surveys administered before and during the study showed that patients had improved social interaction and alertness behavior, improved sleep and rest, mobility and communication. Pain and depression surveys showed a diminishment in pain scores at certain points during the therapy, and that OGF did not induce depression, but may have actually prevented the development of depression in the terminally-ill patients.

"Although this study was not intended to examine tumor response or survival, our preliminary results showed two patients with spread of the cancer to the liver responded with loss of metastases, and survival was increased from 5.6 months under the typical treatment with gemcitabine, to 9.1 months with OGF," Zagon said. "Some patients survived from 21 to

23 months."

Zagon said preclinical studies of OGF indicate that it may be useful in the treatment of other cancers that rely on OGF for growth such as colon, head and neck, kidney and developing nervous system.

Opioid growth factor tonically inhibits human colon cancer cell proliferation in tissue culture.

Native opioid peptides serve as growth factors in a number of normal and neoplastic cells and tissues, including the prevention and delayed growth of human colon cancer xeno-grafts in nude mice. This study examined the hypothesis that opioids exert a direct inhibitory influence on tumor cell growth by the use of a tissue culture model. The naturally occurring pentapeptide [Met5]enkephalin depressed growth of HT-29 human colon cancer cells from 17 to 41% at 12-72 h after administration of 10(-6)M concentration; consistent with previously defined nomenclature, this peptide was termed opioid growth factor (OGF). OGF action exhibited a dose-response relationship, was reversible and not cytotoxic, and was opioid receptor mediated.

Growth inhibition by OGF was not dependent on serum, and was noted in the two other human colon cancer cell lines examined WiDr and COLO 205. This peptide continually repressed growth because an increase in cell number was noted when cells were exposed to the potent opioid antagonist **naltrexone** or an antibody to OGF. Both OGF and its receptor, zeta (zeta), were found in colon cancer cells by immunocytochemistry, and receptor binding assays revealed a nuclear-associated receptor with a dissociation constant of 8.9 nM and a maximum binding capacity of 43 fmol/mg of protein. OGF was produced and secreted by the tumor cells. These results lead to the suggestion that OGF has a direct, tonic, inhibitory action on the growth of human colon cancer cells and contribute to our understanding of the mechanisms underlying the marked antitumor effect of this peptide in nude mice inoculated with human colon cancer cells.

Gemcitabine is the standard of care for advanced pancreatic neoplasia, and exerts its effect through inhibition of DNA synthesis. However, gemcitabine has limited survival benefits. Opioid growth factor (OGF) is an autocrine-produced peptide that interacts with the nuclear receptor, OGFr, to inhibit cell proliferation but is not cytotoxic or apoptotic. The present study was designed to examine whether a combination of chemotherapy with gemcitabine and biotherapy with OGF is more effective than either agent alone in inhibiting pancreatic cancer growth in vitro and in vivo.

The combination of OGF (10^{-6} M) and gemcitabine (10^{-8} M) reduced MIA PaCa-2 cell number from control levels by 46% within 48 h, and resulted in a growth inhibition greater than that of the individual compounds. OGF, in combination with 5-fluorouracil, also depressed cell growth more than either agent alone. The action of OGF, but not gemcitabine, was mediated by a **naloxone**-sensitive receptor, and was completely reversible. OGF, but no other endogenous or exogenous opioids, altered pancreatic cancer growth in tissue culture.

The combination of OGF and gemcitabine also repressed the growth of another pancreatic cancer cell line, PANC-1. MIA PaCa-2 cells transplanted into athymic mice received 10 mg/kg OGF daily, 120 mg/kg gemcitabine every 3 days; 10 mg/kg OGF daily and 120 mg/kg gemcitabine every 3rd day, or 0.1 ml of sterile saline daily.

Tumor incidence, and latency times to tumor appearance, of mice receiving combined therapy with OGF and gemcitabine, was significantly decreased from those of the control, OGF, and gemcitabine groups. Tumor volumes in the OGF, gemcitabine, and OGF/gemcitabine groups were markedly decreased from controls beginning on days 14, 12, and 8, respectively, after tumor cell inoculation. Tumor weight and tumor volume were reduced from control levels by 36–85% in the OGF and/or gemcitabine groups on day 45 (date of termination), and the group of mice exposed to a combination of OGF and gemcitabine had decreases in tumor size of 70% and 63% from the OGF or the gemcitabine alone groups, respectively. This preclinical evidence shows that combined chemotherapy (e.g.

gemcitabine) and biotherapy (OGF) provides an enhanced therapeutic benefit for pancreatic cancer.

Therapeutic applications

Upregulation of OGFr and consequent stimulation of the OGF-OGFr system are important for the anti-proliferative effects of imidazoquinoline drugs like imiquimod and resiquimod, which are immune response modifiers with potent antiviral and antitumour effects, used as topical creams for the treatment of skin cancers and warts.

DOSING

In addition to producing endorphins, the body also produces enzymes which break down endorphins. These are known as endorphinase or enkephalinase.

In order to ensure a lasting effect, OGF has to be administered at regular intervals. Different dosing schedules are used depending on the estimated 'tumor burden' in the body.

Clinical Research carried out at Hershey Medical Center has successfully completed Phase 1 trials and is now in the midst of Phase 2 trials. The doses used are either 250 micrograms per k.g. of bodyweight, via intravenous infusion (once or twice weekly), or 50 micrograms per k.g. of bodyweight, via subcutaneous injection (twice daily).

Conclusion

OGF appears to be an extraordinarily promising agent in the therapy of cancer. Phase I studies have determined an excellent safety profile, which is practically unrivaled in the field of oncology therapeutics.

Furthermore, OGF has been demonstrated to exert beneficial effects on the immune system, thus eliminating fears of long-term damage to the body and immunity.

Since OGF is not a patentable substance, no incentive exists for commercial sponsorship of further human studies. Rather, most of the sponsorship to date has been from governmental sources.

Commercial exploitation of the benefit of OGF is planned through the development of OGF analogues (agents which mimic its action). Such analogues are patentable and therefore provide an incentive for financial investment by pharmaceutical companies which stand to profit from future sales.

Availability

One source for OGF is Biofactor GMBH in Germany, where it is sold under the name LUPEX®. LUPEX® is intended for human use in cancer, AIDS and Autoimmune diseases, Biofactor Tel +49 5322 96 05 14, Fax +49 5322 30 17. Their email is **info@biofactor.de**
The material Biofactor use is not cGMP grade, and therefore is only suitable for subcutaneous injection, and not for intravenous infusion.
Another source for OGF is Netzah Israel Pharmacy in Tel Aviv, Israel. Their Fax number is +972-3-7617329. Their email is **pharmacy@medinisrael.com**
The material which Netzah Israel Pharmacy use is cGMP grade, and therefore it is suitable for both subcutaneous and intravenous administration.