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Earthworms: Harnessing one of natures cancer killers

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Research has proven that invertebrates are immune to malignant disease. We are on the cusp of discovering how their immunopotent systems can serve as anticancer agents.

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Earthworms have a long and provocative association with medicine. They are used as a remedy for smallpox in Burma and Laos, while in Iran earthworms are eaten with bread in order to expel bladder stones. Closer to home, the Nanticoke Indians of Delaware use them to relieve pain associated with rheumatism (*J Am Folklore* 14:30-38, 1901; *J Wash Acad Sci* 41:229-235, 1951).

Earthworms still have a place in the modern world of alternative medicine, most notably as a potential form of cancer treatment. Their curative power may lie in the fact that earthworms, like many invertebrates, are immune to malignant disease (*J Natl Cancer Inst* 31:655-669, 1969).

Indeed, the cells of the earthworm's immune system have shown an ability to actually kill cancer cells. In one study, the cancer cell K562 was grown cultured with immunopotent earthworm cells. The small cells of the latter instantaneously recognized the foreign cancer cells, threw out their voracious false feet (pseudopodia), and began the process of devouring, pulling, and chewing, leading to cell death. Next, a larger cell mops up the battle-scarred terrain, much as monocytes and neutrophils do during inflammation in humans (*Endeavor* 4:160-165, 1981; *Immunology of Annelids*, CRC Press, Boca Raton, Fla., 1994; *Cell Immun* 166:113-122, 1995; *Exp Cell Res* 224:174-182, 1996; *Eur J Cell Biol* 70:278-288, 1996).

This groundbreaking in vitro approach has inspired further research using human, canine, and rodent in vivo systems. The primary goal is to identify the molecule or molecules in earthworm cells that are responsible for cellular confrontation. Moreover, there is a multitude of factors that drive earthworm-mediated response to explore, such as the composition of earthworms themselves, their molecular mechanism, and variability within species.

Killing cancer by humoral mediation

Based on research done in Asia and Europe, one factor that may inhibit the spontaneous growth of tumors is lombricine, which is a phosphagen unique to earthworms. In 1991, investigators at Meiji University in Kanagawa, Japan, analyzed the effects of lombricine, extracted and purified from earthworm skin (*Lumbricus terrestris*), on the growth of palpable, approximately 5 mm, spontaneous mammary tumors in SHN mice.

In the first experiment, daily subcutaneous injections of lombricine (0.3 mg in 0.05 mL olive oil) were found to markedly inhibit the growth of tumors, and were associated with the retardation of the growth of preneoplastic mammary hyperplastic alveolar nodules. In 1H-NMR spectra, the experimental mice had lower serum levels of lactic acid and glucose than controls. By contrast, urine of the experimental group in the above study contained higher levels of allantoin, creatine, and creatinine.

In the second experiment, lombricine given as a dietary supplement (120 mg/kg) also inhibited tumor growth, although less significantly than after injection. This treatment exerted little effect on 1H-NMR spectra of either serum or urine and normal and preneoplastic mammary gland growth (*Anticancer Res* 11:1061-1064, 1991).

When viewed critically, these results suggest that inhibition by lombricine of mammary tumor growth is at least partly due to the maintenance of homeostasis of the body. This includes regulation of excess glucose uptake as a source of energy and nutrition.

G-90 force

Another mediator that retards mouse tumors in vivo is glycolipoprotein. Researchers from the University of Zagreb in Croatia and Beijing University in China isolated a biologically active glycolipoprotein from a whole earthworm (*Eisenia foetida* and *L rubellus*) tissue homogenate and named it G-90. They found that G-90 altered murine cell growth rate in vitro, in a dose-dependent manner, and slowed murine tumor growth in vivo. G-90 does not contain mutagens or carcinogens (*Comp Biochem Physiol Comp Physiol* 102:441-447, 1992; *Chinese Journal of Biochemistry and Molecular Biology* 14:721-725, 1998).

There are several functions attributed to G-90. It possesses growth factors that stimulate proliferation in cell cultures, including an insulin-like growth factor, an immunoglobulin-like growth factor, and two serine peptidases with a tyrosine code and epidermal growth factor (*Adv Exp Med Biol* 546:359-389, 2004).

Epithelial growth factor (EGF) plays an important role in the regulation of cell growth, proliferation, and differentiation by binding to its receptor (EGFR). No published studies link a putative receptor associated with G-90 and EGF, but G-90 has two associated proteolytic enzymes (PI and PII) that engage strongly in fibrinolytic and anticoagulative activities.

Earthworm enzymes and liver cancer

Hepatocellular carcinoma is the fifth most common cancer and the third leading cause of cancer-related mortality worldwide, so continued investigations into how to prevent and manage the disease are desirable. From an evolutionary viewpoint, we know that invertebrate animals have effective, nonspecific innate immune systems but no adaptive system like that of vertebrates. What is critical is that invertebrates rarely, if ever, develop true metastasizing tumors.

Invading surrounding tissues and metastasizing from the primary site to other sites through blood vessels is a crucial characteristic of cancerous cells. Adhesion to the basement membrane, degradation of extracellular matrix (ECM), and transmission of cells in the blood are essential steps in expanding tumor invasion and metastasis. Matrix metalloproteinases (MMPs) are families of zinc-dependent endopeptidases that selectively degrade and remove most of the ECM components of tumors, including collagen and other structural molecules. MMP-2 is constitutively expressed and participates in remodeling ECM. This promotes angiogenesis in tumors and facilitates invasion and metastasis (*Focus: Allergy Research Group* newsletter, March 2009, www.allergyresearchgroup.com).

Earthworm fibrinolytic enzyme (EFE) is a complex protein enzyme widely distributed in the earthworm *E foetida* that can suppress tumor growth in mice inoculated with sarcoma 180 and Ehrlich ascites tumors. EFE possesses significant antitumor activity for certain hepatoma cells, both in vitro and in vivo, and induces apoptosis. Moreover, there is decreased MMP-2 secretion by these cells.

These remarkable characteristics suggest that EFE has potential as a pharmacologic agent; it is readily available, has minimal side effects, and can be extracted at a minimal cost. Coagulation augments metastasis so inhibiting coagulation could drastically reduce metastasis (*Chin Med J* (Engl) 120:898-904, 2007).

Final thoughts

What are some of the factors that make earthworms and other invertebrates immune to metastasizing cancers? One theory holds that the life span of invertebrates is so short there is no time for cancer to develop: Would this then suggest that longer life expectancy is associated with a greater incidence of cancer? Another possibility is that when confronted by foreign matter, invertebrates rapidly deploy an array of leukocytes that secrete lytic, destructive molecules and destroy cell membranes.

Long before modern Western medicine and the advent of the pharmaceutical industry, the animal kingdom was mined for its medicinal resources. Invertebrates are worthy of continued study. The role of earthworms in the destruction of cancer cells is promising. There is certainly a need for more in vitro analysis and animal model studies before definitive clinical trials are initiated.