Regulation of cell proliferation by the OGF-OGFr axis is dependent on nuclear localization signals

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Researchers at The Pennsylvania State University College of Medicine, Hershey, Pennsylvania have discovered that the efficacy of the Opioid Growth Factor (OGF, [Met5]-enkephalin), a clinically important antitumor agent, is dependent on nucleocytoplasmic translocation and reliant on the integrity of nuclear localization signals in the OGF receptor (OGFr).

This discovery, reported in the May 09 issue of *Experimental Biology and Medicine*, provides new insights into the mechanism of an important endogenous system that serves as a tonically active, constitutively expressed, inhibitory regulator of DNA synthesis. This valuable information not only may contribute to understanding the etiology and pathogenesis of diseases related to this native biological system, but to the development of new agents that will enhance effectiveness in treatment.

Previous immunohistochemical and immunoelectron microscope studies have detected OGF and OGFr in both the cytoplasmic and the nuclear compartments. The OGF-OGFr axis is known to regulate cell proliferation by modulating cyclin dependent kinase inhibitors, resulting in a retardation of cells at the G1-S interface of the cell cycle. To address the question of the location and temporal relationships of OGFr nucleocytoplasmic trafficking, a probe of OGFr fused to green fluorescent protein (eGFP) was constructed. Experiments with a human

cancer cell, a squamous cell carcinoma of the head and neck, revealed that translation of OGFr required approximately 5 hours, and transit into the nucleus took 8 hours; OGFr remained in the nucleus for up to 8 days. Transport through the nuclear pore and repression of cell proliferation required two of the three nuclear localization signals (NLS) in OGFr. These results show that the pathway for regulating the cell cycle by the OGF-OGFr complex involves the shuttling of the peptide-receptor complex from the cytoplasm to the nucleus, as well as transport receptors.

The research team was comprised of Dr. Ian S. Zagon, Distinguished University Professor, and Dr. Patricia J. McLaughlin, Professor, along with a postdoctoral fellow Dr. Fan Cheng, in the Department of Neural & Behavioral Sciences. Drs. Zagon and McLaughlin discovered the growth related activity of endogenous opioids, identified OGF as the specific peptide, cloned and sequenced OGFr, and collaborated on demonstrating the remarkable properties of these native peptides in a variety of clinical studies. OGF has proven successful in a Phase I clinical, trial, and Phase II trials for pancreatic cancer and squamous cell carcinoma of the head and neck are in progress.

Co-author Dr. McLaughlin states: "Given the extraordinary biological control of the cell cycle by the OGF-OGFr axis, it may be envisioned that either a loss or a gain in transport shuttling pathways could contribute to the onset and progression of disease." Dr. Zagon adds that "The clinical implications of the study speak to whether changes in nucleocytoplasmic machinery related to the OGF-OGFr axis, part of the body's own machinery governing physiological processes, may be involved with understanding the etiology and pathogenesis of human disease, as well as the basis for the treatment of human disorders."

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine* said "Zagon and colleagues have discovered that the Opioid

Growth Factor (OGF, [Met5]-enkephalin), a clinically important antitumor agent, is dependent on shuttling of the peptide and the OGF receptor from the cytoplasm to the nucleus. This discovery may provide valuable information to understanding the etiology and pathogenesis of diseases related to this native biological system, as well as to development of new agents that will enhance treatment effectiveness".

Source: Society for Experimental Biology and Medicine (news : web)