Regulation of cell proliferation is dependent on nucleocytoplasmic trafficking

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Researchers at The Pennsylvania State University College of Medicine, Hershey, Pennsylvania have discovered that the Opioid Growth Factor (OGF, [Met5]-enkephalin) and its receptor, OGFr, a clinically important system with potent antitumor properties, has controlled entry from the cytoplasm to the nucleus. The nucleocytoplasmic passage of OGF-OGFr is critical to cell proliferation and suggests that there are hierarchical levels of nuclear import. This discovery, reported in the September 2010 issue of *Experimental Biology and Medicine*, provides new insights into understanding the pathobiology of diseases related to this native biological system, and contributes to the development of new agents that will enhance treatment effectiveness.

Previous immunohistochemical and immunoelectron microscope studies have detected OGF and OGFr in both the cytoplasm and the nucleus. 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. Experiments utilizing a human cancer cell line, a squamous cell carcinoma of the head and neck, and a probe of OGFr fused to green fluorescent protein (eGFP), revealed the presence of a transport factor, karyopherin β, which plays a key role in nucleocytoplasmic transport.

Moreover, directionality of transport for karyopherin β is dependent on the small guanosine triphophatase (GTPase) Ran. Knockdown of karyopherin β or Ran with siRNAs, but not the adaptor molecule karyopherin α, prevented transport of OGFr-eGFP and resulted in a

marked increase in DNA synthesis. These results document that the pathway for regulating the cell cycle by the OGF-OGFr axis involves the timely and faithful translocation of this peptide-receptor complex across the nuclear envelope. This nucleocytoplasmic trafficking is critical for cell proliferation.

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 cell proliferative properties of endogenous opioids, identified OGF as the specific opioid peptide involved, and cloned and sequenced OGFr. Along with Dr. Cheng, they have documented that OGF enters cells by clathrin-mediated endocytosis, showed that the OGF-OGFr complex undergoes nucleocytoplasmic trafficking which is dependent on nuclear localization signals, and collaborated on demonstrating the remarkable properties of these native peptides in a variety of clinical studies. OGF has proven successful in Phase I and Phase II clinical trials for pancreatic cancer, and safety and efficacy studies for squamous cell carcinoma of the head and neck, and hepatocellular carcinoma are in progress.

Co-author Dr. McLaughlin states "Given the extraordinary multifaceted and subtle biological control of the cell cycle by the OGF-OGFr axis, it may be envisioned that either a loss or a gain in nucleocytoplasmic transport could contribute to the onset and progression of disease. Localization of these proteins in the wrong cellular compartments could result in pathological states. " Dr. Zagon adds that "The clinical implications of the study speak to whether changes in factors related to the nucleocytoplasmic pathway of the OGF-OGFr axis, part of the body's own machinery governing physiological processes, can be mobilized in treatment of human disorders. Enhancement of these elements could prove extremely effective in reducing abnormal

responses associated with cell proliferation as in inflammation, autoimmune diseases, and cancer."

Dr. Steve Goodman, Editor-in-Chief of *Experimental Biology and Medicine* stated "Ian Zagon and his colleagues are responsible for the describing the myriad of functions of the Opioid Growth Factor (OGF) and its receptor (OGFr) in health and disease. In this very interesting article, they have demonstrated the molecular mechanisms underlying nuclear import of OGF-OGFr. Specifically, they have demonstrated a role for karyopherin β and Ran in this process. The nuclear transport of OGF-OGFr is critical for the regulation of cell proliferation."

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