Medical Xpress

# Nuclear export of opioid growth factor receptor is CRM1 dependent

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In a study in the February 2016 Issue (241:3) of *Experimental Biology and Medicine* researchers at The Pennsylvania State University College of Medicine, led by Dr. Pat McLaughlin, discovered that a novel biological pathway, the OGF-OGFr axis, regulates cell proliferation in normal and abnormal cells and tissues.

The non-classical opioid receptor, OGFr, was first discovered in the 1980s in neural cancer cells and normal rodent brain through collaborative work with Drs. Ian S. Zagon and Steven R. Goodman, and subsequently was isolated, characterized, and cloned. The molecular and protein structure of OGFr has no resemblance to classical opioid receptors, and is an intrinsically unstructured protein with approximately 78% amino acid identity between mouse, rat, and human. OGFr gene and protein expression has been recorded in cells and tissues arising from all 3 dermal derivatives, and OGFr binding has been measured in a wide variety of developing and adult tissues, as well as more than 30 human cancer cell lines.

Dysregulation of the OGFr has been documented in several human cancers whereby biopsies of advanced-stage tumors have reduced receptor relative to normal or non-malignant tissues. The loss of OGFr limits the effectiveness of its specific inhibitory growth factor ligand, OGF, and the blockade of receptor function with low dosages of antagonists such as naltrexone. Thus intact OGFr is requisite for the OGF-OGFr pathway to mediate cell replication.

Blockade of OGFr by antagonists such as naltrexone has led to a variety of therapeutic interventions. The duration of blockade has impacted many biological pathways. Short-term blockade of OGFr with low dosages of naltrexone is currently being used for treatment of a variety of autoimmune diseases. The impact of this opioid antagonist biotherapy is broad-based. Approximately 52 million individuals in the US may benefit from either low dosages of naltrexone or complete receptor blockade for treatment of cancer, multiple sclerosis, inflammatory bowel disorders, or complications associated with diabetes. Worldwide, the potential audience that could benefit from biotherapeutics related to modulation of the OGF-OGFr axis approaches more than 350 million. Knowledge of the mechanism and pathways of OGFr can be used as a diagnostic for dysregulation of the OGF-OGFr regulatory pathway in a variety of diseases. It is anticipated that drug discovery researchers will identify specific and selective receptor antagonists that can be used as safe, inexpensive treatment of these disorders.

OGFr is required to translocate into the nucleus to facilitate its role in cell cycle regulation, and does so utilizing nuclear localization signals, and β and Ran proteins. However, the mechanism of OGFr export was unknown. The discovery, reported in the February 2016 issue of Experimental Biology and Medicine, provides the first evidence that OGFr export is CRM1 (chromosome region maintenance 1; aka exportin1 or Xpo1) dependent. The present study demonstrated in COS-7 (primate fibroblast-like) cells that endogenous, as well as exogenous OGFr accumulates in the nucleus following treatment with leptomycin B, indicating that OGFr is exported in a CRM1 dependent manner. The OGFr sequence contains one predicted nuclear export signal at residues 217-225. Examination of poly-ubiquination sites ruled out OGFr degradation in the nucleus and confirmed proteasome degradation of the receptor in the cytoplasm. Dimerization of OGFr also was not involved in export.

As Dr. Nancy Kren, who conducted the research for her doctoral thesis and is continuing postdoctoral study at the University of North Carolina explains, "What is particularly exciting about this is that the inhibitory effects of the OGF-OGFr axis are also dependent on an intact nuclear export signal. Moreover, the inhibitory function of OGFr appears to require 7 tandem repeats found in the c-terminus that are unique to the OGFr protein." The novelty of these tandem repeats may lead to the identification of novel nuclear export pathways, and may also open new avenues of research for how OGFr is dysregulated in human disease.

As Dr. McLaughlin, Professor at Penn State College of Medicine, and senior author on this research and thesis advisor to Nancy Kren, suggests, "Our laboratory has extended our 30-year study of OGFr to now understand the mechanism of nuclear export. We are particularly interested in future work on these pathways in order to understand the role of the OGF-OGFr axis in a variety of diseases including cancer, autoimmune dysfunction, and complications to diabetes".

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said "the discovery of the role of CREM1 in the nuclear import of OGFr is another major finding by Pat McLaughlin and her colleagues. This is an important step towards understanding the role of OGF-OGFr in normal cellular homeostasis and a wide variety of diseases."

**More information:** N. P. Kren et al. Featured Article: Nuclear export of opioid growth factor receptor is CRM1 dependent, *Experimental Biology and Medicine* (2015). DOI: 10.1177/1535370215605585

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