ImmunoTools *special* Award 2015

Alexandra Schoos, Mag. Ph.D.-student

Supervisor: Ass.Prof. PD Dr. med.vet.habil. Daniela A. Fux

Institute of Pharmacology and Toxicology/Clinical Pharmacology, University of Veterinary Medicine, Veterinärplatz 1, 1210 Vienna, Austria

Role of G-protein-coupled receptors in tumor angiogenesis

G-protein-coupled receptors (GPCRs) represent the largest family of cell surface receptors, which are stimulated by a variety of hormones and neurotransmitters. Through activation of highly different intracellular signaling pathways, GPCRs are involved in the regulation of many vital functions including cellular metabolism and differentiation, growth, neurotransmission, and immune responses.

Due to their central function in physiological processes, modulation of GPCR activity by either agonists and/or antagonists represents a successful and established strategy for the treatment of various disorders of the cardiovascular, respiratory, metabolic, urogenital, and central nervous system.

Recently, GPCRs have been revealed to also play a pivotal role in the progression of multiple malignancies. Analysis of cancer samples from human patients demonstrated an aberrant expression and activity of GPCRs. In-vivo and in-vitro experiments uncovered that the chemokine receptor type 4 (CXCR4) triggers the growth of ovarian as well as head and neck cancer.

GPCRs mediating the physiological effects of the luteinizing hormone or the thyroid stimulating hormone were identified to process the growth of testicular and thyroid cancer, respectively. G-protein-coupled prostaglandin receptors are implicated in metastasis of prostate and non-small-cell lung cancer, whereas activation of the thrombin receptor was observed to support growth and metastasis of mammary malignancies through the initiation of tumor angiogenesis. Interestingly, tumor angiogenesis is also seen for prostaglandin and CXCR4 receptors, so that this process is suggested to be a key step in GPCR-modulated tumor progression.

The signaling mechanism underlying the angiogenic GPCR effect involves activation of the Phosphoinositide-3-Kinase (PI3K)/AKT and the Extracellular-Signal Regulated Kinases ERK1/2 cascade leading to the expression of the vascular endothelial

growth factor (VEGF). VEGF is a highly potent angiogenic factor, which is generated by malignant cells as well as by tumor-associated macrophages and endothelial cells.

These cellular components of the tumor microenvironment also exhibit GPCRs that are coupled to the PI3K/AKT and/or ERK1/2 cascade, so that targeting these "angiogenic receptors" by respective antagonists would represent a promising strategy to prevent GPCR-mediated cancer progression.

However, this concept is strongly limited as the pattern of GPCR expression underlies dynamical changes during tumor progression. Consequently, susceptibility of malignancies to therapeutically used antagonists may be strongly reduced. This phenomenon is facilitated by cytokines and growth factors that are synthesized and released by tumor cells to induce GPCR expression in both malignant as well as in tumor-associated cells in an auto- and paracrine manner.

To aim GPCRs as successful therapeutical drug targets, cytokines and growth factors from individual cancer types have to be analyzed for regulation of GPCR expression. By using ImmunoTools ELISA we intend to examine the cytokine secretome profile of different tumor cells.

To further dissect the role of various tumor-cell derived factors in GPCR expression, recombinant cytokines and growth factors from ImmunoTools will be used to test for GPCR expression in malignant cells, macrophages and endothelial cells. Thus, ImmunoTools will help to uncover potential drug targets interfering with GPCR-mediated tumor progression.

ImmunoTools *special* AWARD for **Alexandra Schoos** includes 25 reagents

recombinant human cytokines: rh IL-4, rh IL-6, rh IFN-gamma, rh sRANKL, rh VEGF-121, rh VEGF-A/VEGF-165

human ELISA-set, human IL-4, human IL-6, human TNF-a, for 96 wells, (each 3 reagents)

mouse ELISA-set, mouse TNF-a, for 96 wells, (each 3 reagents)

recombinant mouse cytokines: rm IL-4, rm IL-6, rm sRANKL, rm TNF-a, rm VEGF

recombinant canine cytokines: IL-3

DETAILS more AWARDS