ImmunoTools *special* Award 2014

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The role of opioids in tumour biology

Opioids are potent analgesic drugs which are commonly used in cancer patients for pain management. Besides their beneficial inhibitory effect on nociception, opioids have been revealed to exert also serious side effects on malignancies especially lung, breast and liver carcinomas. These include promotion of tumour growth by stimulating cell proliferation, metastasis by inducing cell migration, and therapy resistance to anti-neoplastic drugs through the generation of cytoprotective processes. The development of strategies to prevent these opioid side effects proves difficult as the underlying signalling mechanisms of these alternative opioid effects are not identified so far.

Opioid effects are mediated by transmembrane δ, κ and μ (delta, kappa and mu) opioid receptors, which belong to the family of G-protein coupled receptors. After opioid binding, receptor-associated G-proteins become activated at the inner side of the plasma membrane and interact with various intracellular effector proteins, which finally modulate adequate cellular responses to opioid challenge. In addition to this traditional intracellular signalling process, we recently uncovered an *inside-out* signalling pathway driven by stimulated opioid receptors. We found that opioids may activate an intracellular mechanism, which results in the release of various membrane-bound cytokines. These cytokines subsequently bind to the extracellular domain of neighbouring receptor tyrosine kinases (RTK) followed by an activation of their intrinsic kinase activity. This process of so-called RTK transactivation has been demonstrated for epidermal growth factor receptors (EGFR), insulin-like growth factor-1 receptor (IGF-1R) and Tyrosine-kinase A (TrkA) receptor in different cellular settings after opioid receptor stimulation.

It is well established that RTKs play a pivotal role in tumour development and progression. Besides gain-of-function mutation(s), a constitutive auto/paracrine stimulation of EGFR, IGF-1R or platelet-derived growth factor receptors (PDGFR) has been immanent in a variety of human cancers. The corresponding permanent activation of the receptor-downstream ras/raf/ERK, PI3K/Akt and/or JAK/STAT signalling pathways finally translates cytokine signals into enhanced cell proliferation, migration and survival – characteristics of malignant tumour cells.

These facts prompted us to investigate the role of opioid-induced cytokine signalling for their malignant effects. Using different cancer cell lines we intend to find out which cytokine pathway may be activated by opioids via autocrine RTK transactivation. Cytokines provided from ImmunoTools will be thus very useful 1) to characterize the signalling potency of different RTKs in various cancer cells, 2) to determine consequences of cytokine-mediated RTK activation in tumour cells, 3) to evaluate the dominant and alternative cytokine pathways in our cell systems and 4) to finally find out whether malignant opioid effects originate from stimulation of distinct cytokine/RTK signalling pathways.

ImmunoTools will help to gain insights into the signalling mechanisms regulated by opioids in tumour cells and will thus open novel aspects concerning the role of the endogenous opioid system in malignancies. This will serve as basis to develop strategies for safe use of opioids in pain management of cancer patients.

ImmunoTools *special* AWARD for **Sabrina Tripolt** includes 25 reagents

recombinant human cytokines: rh EGF, rh FGF-a / FGF-1, rh FGF-b / FGF-2, rh HGF, rh IFNgamma, rh PDGF-AA, rh PDGF-BB, rh TNFα, rh TPO, rh VEGF-A/VEGF-165,

recombinant mouse cytokines: rm EGF, rm FGF-a / FGF-1, rm FGF-b / FGF-2, rm G-CSF, rm GM-CSF, rm GRO-a / CXCL1, rm GRO-b / CXCL2, rm IFNgamma, rm IL-5, rm IL-6, rm M-CSF, rm PDGF-AA, rm PDGF-BB, rm TNFa, rm VEGF

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