

Venom peptides: emerging biological tools for lung cancer diagnosis

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Many cancers, and the non-small cell lung cancer in particular, are associated with a disturbance of the mechanisms controlling ion homeostasis due, especially, to dysfunction and/or overexpression of many ion channels such as certain subtypes of sodium (Nav1.7) and potassium (KCa3.1) channels, pH-sensitive channels (ASICs for acid sensing ion channels) and nicotinic acetylcholine receptors (nAChRs: $\alpha 7$ and $\alpha 9/\alpha 10$ subtypes). In particular, these ion channels play an important role in cancer cell aggressiveness and tumour invasion, their overexpression likely to be correlated with the development of cancer. Although imaging approaches (radiography, CT-scan or PET-scan) are widely used in the anatomical characterization of lung cancers, some of their limitations require the development of new imaging probes, more specific of overexpressed molecular targets in lung adenocarcinomas. Peptide toxins, which have unique pharmacological properties, are well known to bind selectively and with high affinity on certain ion channels overexpressed in cancerous cells. Therefore, a promising solution towards the development of new lung cancer biomarkers appears to be the chemical synthesis of peptide toxins allowing them to be marked by various fluorescent or radioactive probes using "click" chemistry. Preliminary results by RT-qPCR reveal the overexpression of Nav1.7, nAChRs $\alpha 7$ and $\alpha 9$ in different cancerous cell lines, results that need to be confirmed in lung cancer biopsies. Different couples of toxins/ion channels were explored notably by imaging experiments. For example, confocal microscopy reveals that α -bungarotoxine (α -BgTx), which bind to $\alpha 7$ and $\alpha 9$ nicotinic receptor subtypes are colocalized with the membrane of invasive cancer cells, while Huwentoxin-IV (HwTx-IV), which interacts with Nav1.7, is colocalized at the membrane of all lung cancerous cell lines. Additionally, electrophysiological analysis will be performed to confirm the absence of effect of toxin labelling on their functional property. Following these *in vitro* experiments, *in vivo* analysis will be performed with fluorescent or TEP imaging with xenografted mice. This study will participate to the development of new lung cancer biomarkers.

Keywords: diagnosis, imaging, ion channels, lung cancer, peptide synthesis.
