Ινστιτούτο Οργανικής και Φαρμακευτικής Χημείας
Εθνικό Ίδρυμα Ερευνών

LECTURE

"Genomics of cancer mutations and novel targeted therapeutic"

by

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At the Seminar Room, Ground Floor, at 12:00 o'clock
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48 Vass. Constantinou Avenue, Athens
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"Genomics of cancer mutations and novel targeted therapeutics'

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Abstract

Recent advances towards the blueprinting of the altered molecular networks that lie behind cancer development have paved the way for targeted therapy in cancer. Recent sequencing analyses have shown that 5 to 11 gene important alterations are present in cancers like breast, colon etc. Novel activating mutations in sporadic colorectal cancer (CRC) have been recently identified on major kinase encoding genes such as ***BRAF*** **and** ***PI3KCA***. The presence of these activating point mutations, including the well characterized ***KRAS*** oncogene mutations represent up to 75% of cases in CRC.

A significant part of the research community and of pharmaceutical companies have been oriented to the development of specialized targeted agents, many of which are already available or in clinical trials. The prospect of patient-tailored therapeutic strategies, although close to becoming a reality, raises the level of complexity of the therapeutic approach. **TRAIL**, a cell death inducing cytokine of the TNF family is a promising anti-cancer agent, since it preferentially kills tumour cells.

Here, analysis of RAS and BRAF oncogene specific events as well as global gene expression in physiological as compared to neoplastic cell will be presented. The interplay between oncogenic and apoptotic signals and its exploitation towards uncovering sensitisation pathways to cell death inducing agents like TRAIL, is the other focus of the presentation :

a) **Oncogenic pathway analysis in human colorectal carcinogenesis**

Analysis of gene expression profile during tumour progression in colon cancer cell lines has been performed (Roberts et al. (2006). *Int. J. Cancer* 118, 616–627) Whole genome analysis of RAS and BRAF target genes is currently being performed using the Illumina **microarray platform** (Joyce et al.). RAS and BRAF specific cell and tumour properties are being analysed. We have shown that Ha-RASV12 induces a highly metastatic phenotype **Epithelial to Mesenchymal Transition (EMT)** in colon adenoma cells. This is associated with very high expression of vimentin (Andreolas et al. (2008). *Int. J. Cancer*. In press) as well as with silencing of e-cadherin (Voulgari et al. (2008), under revision).

b) Sensitisation pathways in TRAIL induced cell death in cancer

The interplay between oncogenic ***RAS*** with apoptotic signals induced by the cytokine **TRAIL**, a novel potential cancer therapeutic agent has been analysed using human colon cell lines and freshly isolated primary colon tumour cells. We have shown that **oncogenic forms of *RAS* sensitise** human colon cells to TRAIL induced apoptosis by upregulating TRAIL receptors DR4 and DR5 through a MEK-dependent pathway (Drosopoulos et al. (2005). *J. Biol. Chem*. 280, 22856-22867). We are currently performing rational combination studies of TRAIL with inhibitors of activated kinase pathways, in order to achieve a synergistic effect in cases of resistance. In parallel studies, TRAIL induced apoptosis in **mouse xenographs** of primary colon tumour cells partially due to upregulation of DR5 (Oikonomou et al. (2007). *Br. J. Cancer*. 97, 73 – 84).

c) Chemoprevention in colon cancer

One other goal was the development of exploitable ***in vitro*** **chemoprevention cell systems**, based on the home made inducible oncogene expression systems. In the same study, we have shown that the polyphenol quercetin induced **autophagy** in Ha-Ras transformed cells (Psahoulia et al. (2007). *Carcinogenesis* 28, 1021-1031). In addition, quercetin has been shown to synergise with TRAIL on causing apoptotic death by inducing **accumulation of TRAIL receptors in lipid rafts** (Psahoulia et al., (2007). *Mol. Cancer. Ther* 6, 2591-2599).