PO-006 THE MAPK/C-MYC AXIS IN CRC: NEW PATHOGENIC MECHANISMS AND THERAPEUTIC APPROACHES

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Introduction c-Myc plays a central role in cellular proliferation, differentiation, and apoptosis. Therefore its deregulation represents a powerful trigger of tumorigenesis, particularly in colorectal cancer (CRC). It has been shown that the MEK/ERK pathway phosphorylates c-Myc on serine 62, which stabilises c-Myc by preventing ubiquitin/proteasomal degradation. We recently reported that MEK/ERK inhibition is counteracted by over-activation of p38α MAPK. Here, we identified cellular mechanisms that lead to c-Myc deregulation, which is a crucial issue for improving CRC treatment and survival.

Material and methods The cross-talk between p38α and ERK was assessed in CRC cell lines and in $APC^{Min/+}$ mice, a murine model of familial adenomatous polyposis. To this aim, animals were treated with the p38α inhibitor 4-(4-Fluorophenyl)−2-(4-hydroxyphenyl)−5-(4-pyridyl)−1H-imidazole (SB202190) alone or in combination with the MEK1 inhibitor N-[(2R)−2,3-Dihydroxypropoxy]−3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-benzamide (PD0325901). In order to evaluate the role of p38α and ERK in c-Myc regulation, we used pharmacological inhibitors of these two kinases alone or in combination with inhibitors of the transcriptional mechanism, translational process and proteasome in CRC cell lines. Moreover, the function of p38α and ERK in Myc stabilisation was assessed by genetic ablation.

Results and discussions Here we show that concomitant inhibition of the p38α and MEK/ERK pathways significantly increases the survival of $APC^{Min/+}$ mice in which tumorigenesis is driven by c-Myc deregulation. Genetic ablation of p38α and ERK revealed that these two MAPKs do not regulate c-Myc expression, nor do they affect c-Myc protein translational process. We found that p38α and ERK collaborate in c-Myc stabilisation by inhibiting its proteasomal degradation in CRC cell lines. These results were also confirmed by using the p38α and ERK pharmacological inhibitors LY2228820 (Ralimetinib) and GSK1120212 (Mekinist), respectively, which are currently in clinical trials for inflammatory diseases and cancer.

Conclusion Since c-MYC supports the processes required for normal growth and homeostasis, its ablation is less attractive than modulation of its expression or function. Our results confirmed the essential role of the MAPK/c-Myc axis in intestinal tumorigenesis regulation, suggesting MAPK manipulation as a potential therapeutic approach to counteract c-Myc dependent carcinogenesis.

PO-007 53 INVESTIGATING THE HYPERACTIVATION OF ERK5 SIGNALLING IN SKIN CANCER

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Introduction There are compelling clinical evidences that elevated MEK5/ERK5 signalling in epithelial human tumours correlates with poor prognosis. Accordingly, we have found that ERK5 activation in epithelial cells remodels the inflammatory microenvironment to support cancer development. This is important considering that inflammation is one of the most influential components of most, if not all, tumours. To consider the therapeutic implication of our finding, we have tested the causative link between constitutive ERK5 activation and cancer-related inflammation.

Material and methods We have utilised a novel knock in mouse model carrying a transgene encoding a PGK-Neo-STOP cassette flanked with LoxP sites in front of a constitutive active (ca) mutant MEK5 cDNA (*Wang et al, 2014 J Neurosci 34*). These mice were bred with animals expressing an inducible form of Cre, namely Cre^{ER}, under the control of the keratin 14 (K14) promoter. Induced expression of caMEK5 in keratinocytes was achieved in *K14-*Cre^{ER}*;caMEK5*$^{+/F}$ or *K14-*Cre^{ER}*;caMEK5*$^{F/F}$ offspring by intraperitoneal injections of tamoxifen (every day for 5 days). *CaMEK5*$^{+/F\ or\ F/F}$ littermates were used as controls. Two weeks later, skin tumours were induced by the classical two-stage DMBA/TPA chemical carcinogenesis protocol which gives rise to papillomas, or to DMBA alone to directly induce the formation of predominantly invasive squamous cell carcinomas (SCC).

Results and discussions Our results demonstrated that mutant mice exhibiting hyperactivation of ERK5 in the skin presented a higher tumour burden (number of tumours per mouse) compared with controls. In fact, papillomas appeared earlier, and consequently were noticeably bigger, in *K14-*Cre^{ER}*;caMEK5*$^{F/F}$ animals injected with tamoxifen, than in control littermates. Additionally, we observed that the malignant conversion of papillomas, which normally occurred at a frequency ≤5%–10% with DMBA/TPA treatment, was increased in response to ERK5 hyperactivation. Accordingly, epidermal expression of caMEK5 caused a marked increase in SCC formation upon exposure to DMBA alone.

Conclusion We have found that ERK5 hyperactivation in epidermal keratinocytes increased the sensitivity of the skin to carcinogenesis and the development of malignant tumours. Further studies are currently being undertaken to understand the impact of epidermal expression of caMEK5 on the immune response of the skin to DMBA/TPA exposure.

DNA Damage and Repair

PO-008 ACCELERATED DNA METHYLATION IN GASTRIC MUCOSA ADJACENT TO CANCER AFTER HELICOBACTER PYLORI ERADICATION

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Introduction The molecular irreversibleness with *Helicobacter pylori* (*H. pylori*) infection may have a role in gastric tumorigenesis after *H. pylori* eradication. We performed comprehensive DNA methylation profiling of gastric mucosa after *H. pylori* eradication with or without gastric cancer.

Material and methods Four different groups of biopsies including gastric body from subjects without history of *H. pylori* infection (Hp-: n=23), gastric body from cancer-free subjects after *H. pylori* eradication (cancer-free body: n=48), gastric