Introduction The activity of Vav1 as a mutant oncogene in human tumours has remained questionable for decades. Although mutants of Vav1 were recently identified in human cancers of various origins, the functional activity of these mutants is not fully studied. Vav1 is physiologically active as a GDP/GTP nucleotide exchange factor (GEF) in the hematopoietic system. In this study, we addressed the contribution of several cancer-identified Vav1 mutants to tumorigenic processes.

Material and methods We introduced several amino-acid substitutions at residues identified in human lung cancer as follows: glutamic acid (position 59; calponin homology region) to lysine (E59K); aspartic acid (position 517; C1 domain) to glutamic acid (D517E); and leucine (position 801; carboxySH3) to proline (L801P). The biochemical and transforming activities of these mutants were tested following transfection into NIH3T3 cells.

Results and discussions Among the mutants produced, E59K generated a truncated protein, which preserved its expected size once cells are incubated with MG132, a specific proteasome inhibitor. E59K, D517E and oncVav1 are active as GEF towards Rho/RacGTPases, albeit E59K exhibited the uppermost activity. This result was illustrated by Pymol, a computer software for molecular visualisation, that predicts its increased activity as a GEF. This activity is also manifested in changes in cytoskeleton organisation indicative of transformation. Analysis of protein stability using cycloheximide decay assay revealed that D517E mutant protein is more stable than the other mutants, thus explaining its increased expression and activity. Furthermore, NIH3T3 cells expressing E59K, D517E and oncVav1 mutants exhibited increased cell proliferation, elevated number of transformed foci and increased number of grown tumours in NOD/Scid mice. Of note is the fact that tumours generated by E59K exhibit the most aggressive phenotype among the mutant proteins used in this study, reminiscent of epithelial morphology.

Conclusion Our results convincingly attest to the transforming potential of the Vav1 mutants, E59K and D517E, thus providing compelling evidence that Vav1 mutants can act as ‘real’ oncogenes in human cancer.

LIVER SPECIFIC NEMO ABLATION INDUCES MIXED HEPATOCELLULAR-CHOLANGIOCARCINOMA IN MYC-OVEREXPRESSING MICE

Introduction The MYC oncogene appears to be critically involved in the pathogenesis of HCC. The role of NF-κB in liver cancer is complex, either acts as a tumor-promoter or tumor-suppressor in liver carcinogenesis. However, the role of NF-κB in MYC-induced liver carcinogenesis has not been reported. In the present study, we have generated a mouse model of MYC-induced HCC with or without liver specific
Dimethyl fumarate modulation of antioxidant response in cancer cells: therapeutic applications

1N Saidu, 2G Noé, 3O Cerles, 4F Batteux, 1) Alexandre. 1Cochin- Inserm U1016 – Crns UMR8104 – Université Paris Descartes, Development Reproduction and Cancer, Paris, France; 2UMR638 CNRS- Université Paris Descartes- PRES Sorbonne Paris Cité, Faculté de Pharmacie-, Paris, France; 3Cochin- Inserm U1016 – Crns UMR8104 – Université Paris Descartes, Medical Oncology, Paris, France

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Introduction RAS genes are among the most commonly mutated oncogenes in human cancers, where they have been shown to render resistance to chemotherapy. Hence, there is a current need for therapies targeting KRAS mutated tumours. The mutation of KRAS results in deregulated activation of signalling pathways involved in cell proliferation or survival. Thus, it was shown to induce the activation of nuclear factor erythroid 2 (NF-E2)-related factor 2 (NRF2), which itself controls the expression of a large number of antioxidant enzymes. Dimethyl fumarate (DMF) is a derivative of fumaric acid registered for the treatment of relapsing forms of multiple sclerosis and psoriasis. We previously described an antitumour effect of DMF, which appeared dependent of the inhibition of the antioxidant program driven by NRF2 (Saidu et al. MCT, 2017).

Material and methods We combined in vitro and in vivo methods to examine the effect of DMF on cancer cell death and the activation of the NRF2 antioxidant pathway.

Results and discussions We have shown the effect of DMF on cell death and the activation of the NRF2/DJ-1 antioxidant pathway according to KRAS status (Saidu et al., Oncotarget, 2017). Our data suggests the dependence on NRF2 observed in the mutated KRAS malignant cells makes them more sensitive to the cytotoxic effect of DMF. Moreover, in contrast to malignant cells, our data shows that the same concentration of DMF has no significant cytotoxic effects on non-tumorigenic cells; but is rather associated with NRF2 activation, decreased ROS and increased GSH levels.

Conclusion These results thus open up prospects for the therapeutic use of DMF. They however, also, open up questions such as: how does DMF affect A), NRF2-KEAP1/NRF2-DJ-1 protein interactions? B), other antioxidant proteins? C), are there other NRF2, KEAP1 and/or DJ-1 binding partners that are affected by DMF? To address these questions, we are currently employing tools/techniques such as kinomic analysis, MS, pull-down and co-immunoprecipitation assays; results from which will broaden our understanding on how DMF modulates immune and antioxidant responses in different cancers.

Vegetable semla with addi- ti- on of orange juice, sports and prevention of B- ALL. The current methods and therapies that are used to treat B- ALL are insufficiently targeted and successful. This opens up the need for new therapeutic options. In addition, some patients with B- ALL experience relapses. New approaches are therefore needed to improve the treatment of these patients. The application of synthetic lethal (SL) genes in conjunction with DMF therapy could offer new options for the treatment of B- ALL.

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INVESTIGATING UNUSUAL SYNTHETIC LETHALGENES IN ACUTE LYMPHOBlastic LEUKAEMIA

1A Innes*, 1T Barrow, 2E Schwalbe, 3L Fadhel, 1S Gordon. 1Newcastle University, Northern Institute for Cancer Research, Newcastle upon Tyne, UK; 2Northumbria University, Applied Sciences, Newcastle upon Tyne, UK; 3Department of Biology, University of Baghdad, Baghdad, Iraq

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Introduction B-cell acute lymphoblastic leukaemia (B-ALL) is caused by malignant transformation of B-cell progenitors and has multiple genetic subtypes, each characterised by specific genetic abnormalities, including MLL-rearranged and TCF3/ PBX1 t(11;19). Survival for B-ALL is favourable compared to many other cancers, however, there is a need for novel therapeutic approaches that are less toxic and lead to better long term outcome for patients compared to current treatment options. These could potentially be found by identifying subtype-specific synthetic lethal (SL) genes. We have developed a novel bioinformatic approach which uses genome-wide methylation and expression data to identify candidate SL genes in specific genetic subtypes of disease. We aimed to identify candidate SL genes in MLL-rearranged B-ALL, utilising our novel bioinformatics approach.

Material and methods Genome-wide methylation and expression data from patient samples were used to identify candidate genes. Candidate SL genes were knocked down with siRNA in cell lines with/without the corresponding subtype defining genetic abnormality. Apoptosis was measured by Annexin-V staining, and proliferation by cell counts using a specialised flow cytometer. Gene re-expression was performed using a lentiviral construct, co-expressing eGFP.

Results and discussions Surprisingly, in addition to a single candidate SL gene specific for MLL-fusion related B-ALL, our novel bioinformatic analysis also identified two classes of gene