ONCOGENE-INDUCED VULNERABILITIES

Oncogenic signalling profoundly alters how cells respond to their environment, typically putting tumour cells under tremendous pressure to reconcile conflicting cues. For example, tumour cells must re-organise their metabolic pathways to balance competing needs for biosynthetic precursors with energetic homeostasis, commonly while surviving in a milieu of limiting oxygen and nutrients.

Our overarching hypothesis is that such oncogene-induced biological perturbations can be exploited for cancer therapy, even in the absence of direct suppression of driver oncogenes. We use deregulated MYC as our paradigm oncogene coupled with a mixture of candidate and RNA-based screening approaches to identify induced vulnerabilities in vivo and in vitro and are actively exploring several strategies for selective elimination of cells that overexpress MYC.

MYC in cancer

Overexpression of the transcription factor MYC occurs in a huge number of human cancers, arising from almost every tissue type. MYC overexpression may arise from focal or broad chromosomal amplification, gene translocation, enhanced mRNA and protein stability or indeed increased signalling through upstream regulatory factors such as Ras, Notch or Sir2-catenin. In a number of tumour settings, MYC overexpression is sufficient to initiate or exacerbate tumourigenicity and moreover is typically required to sustain the cancer phenotype. A successful therapeutic strategy that exploits MYC overexpression would likely have a tremendous impact on human health.

MYC-induced metabolic vulnerability

As part of a coordinated programme of cell growth required for cell division, MYC engages a number of biosynthetic programmes, prominently including ribosome assembly and protein translation, placing tremendous energetic demand upon the cell. In order to maintain energetic homeostasis, MYC upregulates glucose transporters and glycolytic enzymes, promoting the Warburg effect of limited glucose breakdown, and in parallel induces expression of glutamine transporters and expedites this pathway to maintain the tricarboxylic acid cycle. The energetic strain that MYC deregulation thus places upon the cell is evident in progressive activation of the AMP-activated protein kinase (AMPK), which plays a key role in maintaining energetic homeostasis. AMPK in turn inhibits TORC1 to attenuate the rate of macromolecular synthesis, effectively allowing cells to balance the rate of ATP consumption with that of ATP production. Importantly, the AMPK-related kinase AMPK/NLK is also required for maintenance of ATP homeostasis in cells wherein MYC is overexpressed. NUAK1 plays a specific role in MYC-dependent activation of AMPK and also maintains mitochondrial respiratory capacity. Suppression of NUAK1 thus impairs the ability of MYC overexpressing cells to respond to declining ATP levels, while simultaneously depriving cells of ATP-generating capacity, suggesting that suppression of NUAK1 may be an effective mean to selectively kill cancer cells with high levels of MYC expression.

Additionally, we have now found that NUAK1 plays a key role in protecting against the toxic levels of reactive oxygen species (ROS). ROS are naturally produced as by-products of mitochondrial electron transport chain activity, and the elevated metabolic demand of cancer cells can thus increase ROS production. Paradoxically, hypoxia can also elevate ROS production and is moreover a common feature of most cancers. Tumour cells cope with the threat posed by ROS in part by diverting glucose away from the mitochondrial transport chain activity, and the elevated metabolic demand of cancer cells can thus increase ROS production. Paradoxically, hypoxia can also elevate ROS production and is moreover a common feature of most cancers. Tumour cells cope with the threat posed by ROS in part by diverting glucose away from the mitochondrial transport chain activity, and the elevated metabolic demand of cancer cells can thus increase ROS production. PARADOXICALLY, AMPK activation, in part via transcriptional regulation of multiple proteins involved in the calcium signal transduction pathway, delays the latter response, thereby exposing an intrinsic vulnerability in cancer cells. We have determined that acute inhibition of the antioxidant response pathway, via targeted suppression of NUAK1, eradicates MYC-driven adenocarcinomas in a genetically engineered mouse model of colorectal cancer. All the while providing strong evidence to support targeting NUAK1 in human colorectal cancers, this observation challenges dietary advice commonly given to patients who already have cancer, in that popular consumption of antioxidant supplements may actually benefit the cancer cells more than the patient.

Figure 1 ERBB signaling during progression of KRAS mutant lung cancer

The image shows in situ hybridisation of the ERBB ligand Amphiregulin (Areg, black dot) at the interface between tumour and normal tissue. High expression of Areg may reflect progression from benign to invasive lung cancer but also may predispose responsiveness to broad spectrum ERBB inhibitors.

Oncogenic cooperation in pancreatic cancer

Activating mutations in KRAS initiate almost all cases of pancreatic ductal adenocarcinoma (PDAC), the deadliest form of pancreatic cancer. MYC is an obligate effector of RAS’s oncogenic output, and genetic ablation of even one copy of MYC can dramatically extend the lifespan of KPC mice. In collaboration with Rosalie Sears (Oregon Health Sciences University) and Jennifer Manton, we are examining the role of MYC during pancreatic development to explore potential MYC-induced vulnerabilities that might reveal new therapeutic opportunities. We have shown that a modest elevation of MYC above physiological expression dramatically accelerates onset of PDAC and drives lineage plasticity that is strongly implicated in the severity of this debilitating disease.

Major developments in 2018

We published two primary papers in leading cancer research journals along with six related datasets. Our work identifying a druggable requirement for ERBB activity in KRAS mutant lung cancer was widely reported in the press and highlighted in two Nature Reviews family editorials. The work has generated substantial interest from industry and plans are progressing for a Phase 2 clinical trial in KRAS mutant lung cancer, to be led from Glasgow. Continuous work on the same project has revealed a novel signalling activity between tumour and infiltrating immune populations that may be exploitable for early detection.

Another major scientific development saw the successful publication of a new model for malignant pleural mesothelioma. We additionally published a review on mesothelioma (in collaboration with Dr Kevan Byth) and an editorial on MYC and oxidative stress, and lab members contributed to a publication led by the lab of Dr Giulia Cordero (University of Glasgow). External funding was awarded by the British Lung Foundation to work on mesothelioma (in collaboration with Nick Knighton).

Outreach activities included hosting a student delegation for Southwest Community College, Tennessee; interviews for television, newspaper and online media outlets; publications in a PLoS Funder Jaunt; and invited lectures at MRC Hammersmith, RCS Ireland, Sick Kids Hospital in Toronto and the annual AMPK conference and maintenance of KRAS mutant lung cancer. Our data suggest that KRAS-driven tumours actively seek ways to amplify signalling through the RAS pathway in order to sustain the tumour phenotype. As there are presently no clinically proven small molecule inhibitors of KRAS, our observation raises the exciting possibility that simultaneously inhibiting signalling components upstream and downstream of RAS with existing therapeutic agents may benefit the very large number of lung cancer patients whose disease is driven by mutant KRAS.

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