Myc-induced vulnerabilities/thoracic cancer research

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.

We use genetically engineered mouse models, primarily of lung cancer and mesothelioma, to understand how developing tumours cope with conflicting cues in their natural environment. Our overarching hypothesis is that 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 RNAi-based approaches to identify inducible vulnerabilities in vivo and in vitro and are actively exploring several strategies for selective elimination of cells that oversexpress MYC.

MYC in cancer

Oversexpression of the transcription factor MYC occurs in a vast number of human cancers. The overexpression may arise from focal or broad chromosomal amplification, gene translocation, enhanced mRNA and protein stability, or indeed chromosomal amplification, gene translocation, and oesophageal cancers, indicating widespread pathway has been reproduced in multiple cancer models of Lung Adenocarcinoma. These next generation models will provide exceptional platforms for further investigation of tumour progression and the development of anti-cancer immune responses. Postdoc George Skalia’s efforts were rewarded with a 3-year funded project extension from Merck in collaboration with Cancer Research Horizons.

The year saw a welcome return to in-person conference attendance, with the lab presented posters and for speaking at the European Workshop on Cell Death (Fugli Italy), EACR (Seville, Spain), CSHL Mechanisms & Models of Cancer (CSHL Mechanisms & Models of Cancer Conference (Manchester)). Mice generated in the lab featured in 1 pre-print and 1 publication related to the current all-at-once model systems, with positive acceptance of extending her tenure in the lab to continue her work on disease positioning of immune-visible cancers.

Inflammation and genetics of mesothelioma

Mesothelioma is a lethal cancer of the lining of the chest that arises in people chronically exposed to asbestos. There are no effective therapies and patient survival is typically less than 18 months from diagnosis. Our lab has taken up the Respiratory Pathology network to sustain the tumour phenotype.

As contributors to the MRC National Mouse Genetics Network - Cancer Cluster, we also continued our work on generating an new multi-drug inducible Tandem Arranged Regulator (TARI) allele to enable modelling of sequential genetic events in mice, in contrast to current all-at-once models. We have found that modestly elevating MYC levels in a KRAS-driven model of lung cancer is sufficient to drive tumour progression to a metastatic disease. This progression arises in part through increased transcription of promiscuous ERBB family ligands. We have identified an unexpected requirement for signal transduction through the ERBB receptor tyrosine kinase network for both establishment and maintenance of KRAS-mutant lung cancer. Our data suggest that KRAS-driven tumours actively seek ways to amplify signalling through the RAS pathway to sustain the tumour phenotype.

As part of a coordinated programme of cell growth required for cell division, MYC engages a number of biosynthetic programmes, such as ribosome assembly and protein translation, placing tremendous energetic demand upon the cell. In order to maintain energetic homeostasis, MYC upregulates glucose transporters and glucose-inducible enzymes, promoting the Warburg effect of limited glucose breakdown, and in parallel induces expression of glutamine transporters and exploits this pathway to maintain the citric acid cycle. The energetic strain that MYC deregulation thus places upon the cell is evident in prominent 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 ATP production. Importantly, the AMPK-related kinase NUAK1 is also required for MYC overexpression 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 means to selectively kill cancer cells with high levels of MYC expression.

Oncogene cooperation during lung cancer progression

Lung-cancer remains one of the deadliest forms of cancer worldwide, accounting for 18% of all cancer-related deaths, and the incidence of lung cancer is on the rise, especially in the increasingly industrialised and densely populated cities of emerging economies. Poor prognosis arises in large part from the combination of late disease detection and limited matching of patients with emerging targeted therapies. We have found that modestly elevating MYC levels in a KRAS-driven model of lung cancer is sufficient to drive tumour progression to a metastatic disease. This progression arises in part through increased transcription of promiscuous ERBB family ligands. We have identified an unexpected requirement for signal transduction through the ERBB receptor tyrosine kinase network for both establishment and maintenance of KRAS-mutant lung cancer. Our data suggest that KRAS-driven tumours actively seek ways to amplify signalling through the RAS pathway to sustain the tumour phenotype.

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