ONCOCENE-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 such conflicting cues in their natural environment. 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 RNAi-based 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 ß-catenin. In a number of in vivo settings, MYC overexpression is sufficient to initiate or exacerbate tumourigenesis and moreover is typically required to sustain the cancerous phenotype. A successful therapeutic strategy that exploits MYC overexpression would likely have a tremendous impact on human health. In order to facilitate investigation of physiologically relevant levels of deregulated MYC expression in any tissue, we have generated and characterised Rosa26-lsl-MYCDM mice, which we have used to maintain MYC overexpression in a number of tissue types, including lung and mesothelium. Suppression of NUAK1 thus impairs the ability of MYC-overexpressing cells to respond to declining ATP levels while simultaneously depriving cells of ATP-rich regions, 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 some 15% of all cancer-related deaths, and the incidence of lung cancer is on the rise, especially in the more 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 progression to 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 signaling 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 KRAS with existing therapeutic agents may benefit the very large number of lung cancer patients whose disease is driven by mutant KRAS.

Inflammation and genetics of mesothelioma

Mesothelioma is a lethal cancer of the lining of the chest cavity that arises in people chronically exposed to asbestos. There are no effective therapies and patient survival is typically less than 2 years from diagnosis. My group has teamed up with respiratory physician Kevin Blyth to build an international network of clinicians and researchers with the common goal of improving patient outcomes for this dreadful disease. We have developed a new mouse model of mesothelioma that will enable us to investigate the interplay between asbestos-driven chronic inflammation and the major recurring mutations that are commonly found in human mesotheliomas. Significantly, intra-tumoral injection of asbestos dramatically accelerates onset and severity of mesotheliomas in our mice, even after homologous deletion of three major tumour suppressor genes, including that chronic inflammation continues to contribute to mesothelioma beyond the acquisition of rate-limiting mutations. This startling observation suggests that patients may benefit from interventions that aim to reduce inflammation, in addition to those directly targeting the tumour population.

Major developments in 2020

Oncogene cooperation in evasion of anti-tumour immunity

Our major publication of 2020 revisited the mechanism of oncogenic cooperation of MYC and KRAS in the context of pancreatic cancer. We showed that acute activation of MYC or KRAS in otherwise wild-type fibroblasts elicits largely overlapping transcriptional responses, with genes regulated by MYC comprising a large subset of KRAS-regulated genes. The combination of simultaneous activation of MYC and KRAS increased the potency of gene regulation, extending and deepening the transcriptional responses induced by either alone. Although perhaps not surprising to a core of investigators that follow MYC biology closely, our data contradict a long-standing dogma of MYC and KRAS complementarity which predicted largely non-overlapping transcriptional impacts of these two oncogenes. From pathway analysis, we showed that MYC and KRAS combine to potentially suppress multiple cascades involved in cell communication with the immune system, with downregulation of the Type I interferon pathway and of MHC I-dependent antigen processing and presentation, thus preventing effective transcriptional responses. Importantly, we showed similar suppression of the Type I interferon cascade during MYC-accelerated progression of pancreatic ductal adenocarcinoma xenografts. Moreover, and, perhaps most significantly, we demonstrated that both MYC and KRAS converge to drive STAT3 and PI3K-AKT pathway activation in PDAC. Genetic suppression of MYC or KRAS restored interferon signalling, enabling PDAC tumours to elicit CXCL13 production in nearby macrophages and thereby recruit anti-tumour effector immune cells to limit tumour progression and extend survival. These exciting observations were published in the June issue of Cancer Discovery.

New initiatives

Despite the profound and severely negative impact of COVID-19 on our research activities, we initiated and continue to execute a new active drug discovery programme involving the Institute’s Drug Discovery Unit, CRUK Translational Discovery Labs and Merck pharmaceuticals, financially supported by the latter. This collaboration was initiated by postdoctoral scientist George Skalska, a joint venture of the CRUK Accelerator PRIDICT-Meso, with postdoctoral scientist Katarina Gyuraszova continuing development and characterisation of a new generation of small molecule inhibitors of mesothelioma, greatly assisted by Pooyeh Farahmand and her Geneva colleague, Jennifer Doig. This exciting initiative embeds the group within a large international consortium, and represents a better understanding of progression from benign asbestos-associated pleural inflammation to Malignant Pleural Mesothelioma.

Career Progression

I gained promotion to Professor of Lung Cancer & Mesothelioma within the Institute of Cancer Sciences, University of Glasgow.

Sarah Lean submitted and successfully defended her thesis on development of an immunogenic mouse model of Lung Cancer and subsequently continued in my group as maternal cover for Jennifer Crowe. Indeed, the group welcomed two new postdoctoral scientist positions at the Indian Institute of Technology, Madras, marking the conclusion of an immensely successful postdoctoral tenure in my group. The group collectively wishes Nathiya Madras every success in her future career.

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