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IN BRIEF

TUMOUR MICROENVIRONMENT

Tissue-specific functions

The protease cathepsin B (CTSB) has previously been shown to be crucial for mammary tumorigenesis in the mouse mammary tumour virus–polyoma middle T antigen (MMTV–PyMT) mouse model. Ruffell *et al.* now report that CTSB loss does not affect development of squamous cell carcinomas (SCCs) in mice that express human papillomavirus type 16 (HPV-16) oncoproteins in squamous epithelial cells (K14-HPV-16 mice). Conversely, cathepsin C (CTSC) loss slowed the growth of SCCs in K14-HPV-16 mice, and CTSC loss had no effect on MMTV–PyMT mediated tumorigenesis. Therefore, tissue context is important in defining the functional roles of these enzymes.

ORIGINAL RESEARCH PAPER Ruffell, B. *et al.* Cathepsin C is a tissue-specific regulator of squamous carcinogenesis. *Genes Dev.* http://dx.doi.org/10.1101/gad.224899.113 (2013)

THERAPEUTIC RESISTANCE

Blocking a mutant

Resistance to epidermal growth factor receptor (EGFR) inhibitors in patients with non-small-cell lung cancer (NSCLC) is often caused by acquisition of the T790M mutation in EGFR (EGFR-T790M). Walter *et al.* have developed a kinase inhibitor, CO-1686, that effectively inhibits EGFR-T790M without affecting wild-type EGFR. CO-1686 reduced tumour growth in several preclinical models of NSCLC, including transgenic mice expressing mutant EGFR and xenograft models. CO-1686 is being tested in Phase I/II clinical trials for EGFR-mutant NSCLC.

ORIGINAL RESEARCH PAPER Walter, A. O. *et al.* Discovery of a mutant-selective covalent inhibitor of EGFR that overcomes T790M-mediated resistance in NSCLC. *Cancer Discov.* http://dx.doi.org/10.1158/2159-8290.CD-13-0314 (2013)

TUMOUR MICROENVIRONMENT

Time to decompress

The growth of solid tumour and stromal cells in a confined microenvironment leads to increased pressure within the tumour, which compresses blood vessels and reduces vascular perfusion. The matrix component hyaluronan has been implicated in blood vessel compression before, but Chauhan *et al.* found that collagen is also required, and that production of both of these components can be reduced by the angiotensin receptor blocker losartan, which is commonly used to treat hypertension. Losartan treatment of tumour-bearing mice reduced tumour blood vessel compression and increased vascular perfusion, allowing improved delivery of oxygen and chemotherapy.

ORIGINAL RESEARCH PAPER Chauhan, V. P. *et al.* Angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumour blood vessels. *Nature Commun.* http://dx.doi.org/10.1038/ncomms3516 (2013)

TUMORIGENESIS

Loss of polarity

Atypical protein kinase Cι (PKCι) has several substrates, some of which are involved in establishing epithelial apico-basal polarity. Linch *et al.* identified a domain in PKCι that is crucial for the recruitment of the substrate lethal giant larvae homologue 2 (LLGL2), but not for other substrates such as PAR3. Mutation of this PKCι domain at R471 disrupts epithelial polarity, and, interestingly, recurrent mutations in R471 were identified in human cancers, supporting the importance of polarity loss in tumorigenesis.

ORIGINAL RESEARCH PAPER Linch, M. *et al.* A cancer-associated mutation in atypical protein kinase Cι occurs in a substrate-specific recruitment motif. *Sci. Signal.* **6**, ra82 (2013)