IN BRIEF

TUMORIGENESIS

miRNAs — novel regulators in skin cancer

Zhang, Ge and Fuchs have provided new insights into the role of microRNA-125b (miR-125b) in the initiation, progression and maintenance of squamous cell carcinoma (SCC). Using an inducible mouse model, they found that miR-125b overexpression in skin epithelium promoted spontaneous tumour formation as well as sensitizing skin to chemically-induced carcinogenesis. Furthermore, miR-125b expression maintained tumour growth by repressing differentiation and promoting a cancer stem-cell-like transcriptional programme. By identifying and validating miR-125b targets specifically associated with tumorigenesis, they found that miR-125b directly represses stress-responsive MAPK transcripts. It also indirectly maintains epidermal growth factor receptor (EGFR) signalling, by repressing vacuolar protein-sorting 4 homologue B (*Vps4b*), which encodes a protein that promotes endocytic degradation of phosphorylated EGFR.

ORIGINAL RESEARCH PAPER Zhang, L. *et al. miR-125b* can enhance skin tumor initiation and promote malignant progression by repressing differentiation and prolonging cell survival. *Genes Dev.* **28**, 2532–2546 (2014)

THERAPY

Resisting combinations

Combination therapy with BRAF-V600E and MEK inhibitors is under investigation to overcome resistance to BRAF-V600E inhibitors. However, one-third of patients receiving this combination progress within 6 months. To identify possible mechanisms of resistance, Long *et al.* analysed 20 melanoma metastases with BRAF-V600E from 10 patients treated with dabrafenib (a BRAF-V600E inhibitor) and trametinib (a MEK and ERK inhibitor). They found MAPK reactivation through *BRAF* amplification and activating mutations of NRAS and MEK2. Interestingly, whereas MEK2-C125S mutation conferred resistance to the combination therapy, the equivalent MEK1-C121S mutant did not, highlighting a possible unique function of MEK2. As mutations in the MAPK and PI3K pathway are often already present in BRAF-V600E-mutant melanoma, the authors raise caution about combining BRAF-V600E inhibition with inhibitors of either of these pathways.

ORIGINAL RESEARCH PAPER Long, G. V. *et al.* Increased MAPK reactivation in early resistance to dabrafenib/trametinib combination therapy of BRAF-mutant metastatic melanoma. *Nature Commun.* **5**, 5694 (2014)

METASTASIS

Correlating types of motility with metastasis

Using high-resolution multiphoton microscopy of mammary carcinomas in mice, Gligorijevic *et al.* assessed tumour cell phenotype and the likelihood of metastasis. Slow-moving tumour cells had invadopodia, whereas fast-moving cells did not, and both types of locomotion were present in different regions of the same tumour. Further analyses revealed that only tumour cells in invadopodium-rich environments were able to degrade the extracellular matrix (ECM) and disseminate, and the number of invadopodia correlated with ECM degradation. Inhibiting metalloproteinases prevented ECM degradation and metastasis to the lung. Further understanding of how motile phenotypes correlate with metastasis may improve treatment options for patients.

ORIGINAL RESEARCH PAPER Gligorijevic, B. *et al.* Multiparametric classification links tumor microenvironments with tumor cell phenotype. *PLoS Biol.* **12**, e1001995 (2014)