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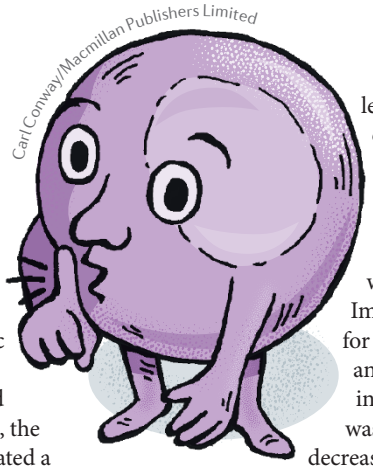
> MSK1 expression was positively associated with luminal, differentiated gene signatures

BREAST CANCER

Staying silent



Bone micrometastases in breast cancer can remain asymptomatic for years, which is typical for breast cancer of the oestrogen receptor-positive (ER^+) luminal subtype. A potential mechanism for this dormancy has been identified by a study published in *Nature Cell Biology*, reporting that loss of the nuclear kinase mitogen- and stress-activated kinase 1 (MSK1) enables latent breast cancer cells to form symptomatic lesions.

To selectively analyse dormant bone metastatic breast cancer cells, the authors injected T47D ER^+ luminal breast cancer cells into the left ventricle of mice and tracked these cells using an *in vivo* imaging micro-computed tomography system. The resultant lesions were chronologically characterized: clinically asymptomatic dissemination of cells into the bone resulted in stable, latent lesions, before becoming overt and symptomatic in a small fraction of mice. Immunohistochemical analysis of latent and overt lesions showed that cells in latent lesions were proliferating less and had higher rates of apoptosis than those in overt lesions, resulting in a steady size of the tumour mass, also referred to as 'tumour mass dormancy'. This model was used in a genome-wide short-hairpin RNA (shRNA) screen, in which shRNA-expressing cells that formed symptomatic bone metastatic lesions were analysed. Based on this analysis, the researchers created a list of candidate genes, silencing of which might promote loss of tumour mass dormancy, while omitting those genes known to be directly associated with cell proliferation or cell death. Among those top-listed genes, the gene encoding MSK1 was selected for further analysis.

Analysis of three independent cohorts of ER^+ breast cancer patients revealed that downregulation of MSK1 gene or protein expression was associated with bone relapse within 5 years of primary tumour diagnosis and lower metastasis-free survival compared with ER-negative breast cancer patients. In a separate analysis of gene expression levels in primary tumours of different breast cancer subtypes, MSK1 expression was positively associated with luminal, differentiated gene signatures, and negatively associated with basal, undifferentiated gene signatures.

shRNA or CRISPR–Cas9 mediated depletion of MSK1 in ER^+ breast cancer cell lines led to increased dissemination of these cells to the bone and formation of symptomatic lesions compared with control cells *in vivo*. MSK1 depletion also led to increased formation of oncospheres *in vitro* compared with control cells. Importantly, the capacity for increased invasion and metastasis initiation in MSK1-depleted cells was accompanied by decreased expression of genes of the luminal gene signature, in particular *FOXA1* and *GATA3*. This decrease in luminal gene expression was also observed in ER^+ patient-derived xenografts with low levels of MSK1. As a nuclear kinase, MSK1 controls gene expression by histone phosphorylation. Indeed, MSK1-depleted cells showed a global reduction in transcriptionally active chromatin regions, including those covering promoters of genes of the luminal gene signature, but excluding those covering promoters of genes of the basal gene signature.

Together, MSK1 maintains the luminal differentiation status of breast cancer cells through epigenetic mechanisms, thereby restraining their metastatic capacity. MSK1 could potentially be used in patient stratification, but this requires further validation.

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ORIGINAL ARTICLE Gawrzak S. et al. MSK1 regulates luminal cell differentiation and metastatic dormancy in ER+ breast cancer. *Nat. Cell Biol.* **20**, 211–221 (2018)