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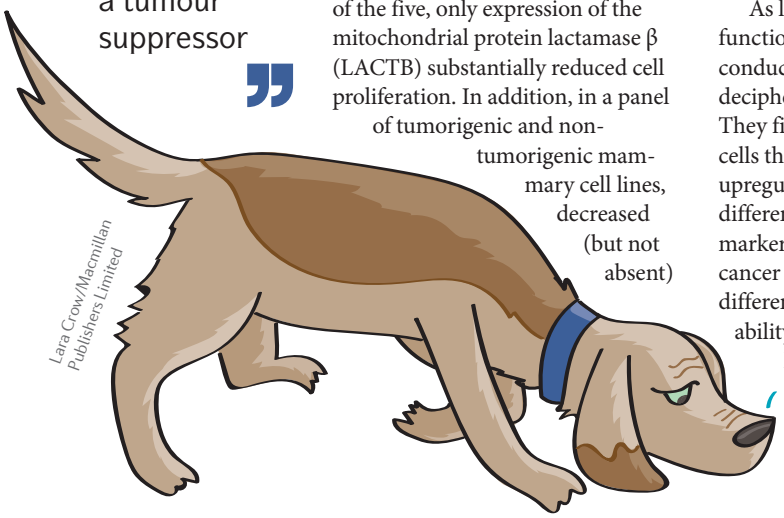
TUMOUR SUPPRESSORS

Following the clues of cancer-resistant tissues

Some tissue or cell types are relatively resistant to tumorigenesis, but the mechanisms underlying this tumour suppression are not well-explored. Using gene expression analyses of cancer-resistant differentiated muscle cells, Keckesova *et al.* have identified a mitochondrial protein that can induce differentiation and suppress proliferation of breast cancer cells *in vitro* and *in vivo*.

The authors first differentiated both mouse and human muscle progenitor cells *in vitro* and analysed mRNA expression levels. Of the genes that were upregulated in differentiated cells compared with undifferentiated cells, five were chosen for further study. Each gene was inducibly expressed in MCF7 breast cancer cells also expressing oncogenic HRAS-G12V (MCF7-HRAS cells); of the five, only expression of the mitochondrial protein lactamase β (LACTB) substantially reduced cell proliferation. In addition, in a panel of tumorigenic and non-tumorigenic mammary cell lines, decreased (but not absent) protein levels of LACTB correlated with tumorigenicity. Similar data were observed in human breast cancer tissue compared with normal breast.

> “LACTB functions as a tumour suppressor”



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To examine the role of LACTB in cell proliferation, the authors first analysed cells with induced LACTB overexpression; this indicated that LACTB reduced proliferation of breast cancer cells without affecting non-tumorigenic mammary cells. Furthermore, if LACTB expression was induced in orthotopic xenograft tumours in mice, tumour size was significantly reduced. Although knockdown of LACTB or HRAS-G12V expression alone in normal mammary cells did not induce tumour formation in mice, the combination of the two did. Together, these data suggest that LACTB functions as a tumour suppressor.

As little is known about the function of LACTB, the authors conducted a series of experiments to decipher its mechanisms of action. They first observed that cancer cells that re-expressed LACTB had upregulated markers of epithelial differentiation but downregulated markers of mesenchymal cells and cancer stem cells, and that these more differentiated cells had a reduced ability to initiate tumours.

LACTB is a mitochondrial protein, and analysis of mitochondrial processes indicated that these were disrupted in MCF7-HRAS cells when LACTB was induced. LACTB has previously been linked to fatty acid metabolism; indeed the mitochondrial lipid classes lyso-phosphatidylethanolamines (LPEs) and phosphatidylethanolamines (PEs) were reduced in MCF7-HRAS cells expressing LACTB. Furthermore, supplementing the culture medium of these cells with LPEs (but not PEs, which cannot be transported into mitochondria) partially rescued both the loss in proliferation and the increase in differentiation markers following LACTB induction, indicating that these processes are connected. The authors hypothesized that LACTB might affect mitochondrial enzymes involved in lipid metabolism. They showed that LACTB expression reduced the levels of phosphatidyl-serine decarboxylase (PISD), which converts phosphatidylserine into PE, and that knockdown of PISD had effects on cells similar to that of LACTB expression. Further evidence supported LACTB's predicted role as a protease; this catalytic activity was required for PISD downregulation, but it is unclear whether PISD is a direct substrate of LACTB.

Although a complete picture of how this metabolic pathway influences differentiation and whether it applies to other cancer types remain to be determined, this study has revealed the potential benefit of looking towards cancer-resistant tissues to identify new tumour-suppressive pathways.

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ORIGINAL ARTICLE Keckesova, Z. *et al.* LACTB is a tumour suppressor that modulates lipid metabolism and cell state. *Nature* **543**, 681–686 (2017)