could inhibit IL-17$^+$ γδ T cells, the authors went on to show that transplantation of B16-F0 cells into mice deficient for NADPH oxidase 2 (NOX2), which generates superoxide, led to an expansion of IL-17$^+$ γδ T cells. Basal levels of the major intracellular antioxidant glutathione as well as several other antioxidants and enzymes involved in ROS detoxification were decreased in IL-17$^+$ γδ T cells compared with IFNγ$^+$ γδ T cells, explaining their sensitivity to oxidative stress. Importantly, human Vδ1$^+$ γδ T cells, which represent the main γδ T cell subset producing IL-17 in human tumours, also exhibit low glutathione levels and are strongly inhibited by ROS in contrast to other human T cell subsets.

This study presents a regulatory mechanism in the TME that could be harnessed to limit the cancer-promoting functions of γδ T cells.

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ORIGINAL ARTICLE Mensurado, S. et al. Tumor-associated neutrophils suppress pro-tumoral IL-17+ γδ T cells through induction of oxidative stress. *PLoS Biol.* **16**, e2004990 (2018)

through miRNA-mediated silencing in ceRNA networks. The key role of these trans effects was confirmed by mathematical modelling.

In summary, pervasive 3′US, which occurs in many cancers, modulates tumour suppressor ceRNA networks and interferes with the ability of ceRNAs to bind and sequester miRNAs, resulting in increased miRNA-mediated silencing of their ceRNA tumour suppressor partners. Overall, this work highlights the emerging importance of ceRNA networks in regulating tumour suppressors.

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CACHEXIA

From rock ‘n’ roll to heavy metal

Cancer-associated cachexia is a severe tissue wasting syndrome. Alleviating the loss of adipose and skeletal muscle tissue would help improve the quality of life of patients who are affected by this syndrome and potentially improve disease outcome. Three recently published studies have identified underlying mechanisms of tissue wasting in early and advanced disease, raising the prospects of therapy options.

Two reports studied tissue wasting in pancreatic ductal adenocarcinoma (PDAC), using mouse models with activation of *Kras* and loss of p53 function (KP mice). Parajuli, P., Kumar, S. et al., who published in *Developmental Cell*, analysed muscle tissue loss in advanced PDAC and found that the transcription factor TWIST1 was required for skeletal muscle cachexia observed in KP mice older than 12 weeks, following overt PDAC formation. TWIST1 was induced in skeletal satellite cells, which triggered a paracrine protein degradation programme in myofibres. Muscle TWIST1 expression was also increased in mouse models of colorectal and lung cancer, and melanoma. In colorectal and lung cancer patients with cachexia, muscle TWIST-1 expression was increased. Activin A, a transforming growth factor-β (TGFβ) family member, induced TWIST1 in vitro, and TWIST1 induced the muscle degradation enzymes MuRF1 and Atrogin1 in mice. TWIST1 activity could be inhibited by the BET inhibitor JQ1, which led to a reversal of muscle cachexia and prolonged survival of KP mice.

Danai, L. V., Babic, A. et al., who published their findings in *Nature*, analysed tissue wasting during early stages of PDAC formation in KP mice and showed that loss of adipose and skeletal muscle tissue occurs by 6 weeks of age, before the frank onset of PDAC. Loss of adipose tissue was specifically linked to reduced exocrine pancreatic function rather than a systemic factor. While dietary supplementation with pancreatic enzymes reduced adipose tissue wasting in KP mice, it surprisingly also reduced the survival of KP mice — raising doubts about whether adipose tissue wasting was causally linked to reduced survival in PDAC patients. Indeed, in a population of 782 PDAC patients, adipose or skeletal muscle tissue wasting was not associated with reduced survival.

The third study looked at metastatic cancer-induced cachexia. In mouse models of metastatic breast, colon and lung cancer, muscle overload with the heavy metal zinc increased muscle tissue wasting by blocking muscle cell differentiation and promoting myosin heavy chain loss. Wang, G., Biswas, A. K., Ma, W. et al., who published their results in *Nature Medicine*, showed that metastatic disease in their models was accompanied by reduction in body weight and loss of muscle tissue. The cachectic muscle tissue showed upregulation of the metal-ion transporter ZRT- and IRT-like protein (ZIP14). ZIP14 was upregulated in cachectic patients, and induced in vitro in response to inflammatory cytokines. ZIP14 mediated zinc influx and muscle cachexia, and was dispensable for tumour growth in mice.

Credit: Lara Crow/Macmillan Publishers Limited

Tumour-dependent changes in protein breakdown and inflammation contribute to and promote cachexia in advanced disease, in which cachexia is common and often associated with poor prognosis. In PDAC, the syndrome can develop even before frank cancer onset owing to functional organ impairment and defective nutrient catabolism. While cachexia might not be linked to patient survival across cancer types and/or stages, the lower quality of life associated with this syndrome necessitates further studies into therapeutic options.

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