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MYC sets a tumour-stroma metabolic loop.

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Abstract

How the metabolic crosstalk between cancer and stromal cells affects tumour growth is incompletely defined. MYC-activated cancer cells are now shown to secrete exosomal *miR-105*, which fuels tumour growth by inducing a MYC-dependent metabolic programme in cancer-associated fibroblasts.

Carcinomas are composed not only of transformed epithelial cells, but also many types of non-tumorous cells, which include fibroblasts, endothelial cells, and immune cells (1). Reciprocal crosstalk between cancer cells and the surrounding stroma plays an important role in carcinogenesis (2). In particular, tumors convert adjacent fibroblasts, the most abundant cell type in connective tissues, into cancer-associated fibroblasts (CAFs). CAFs are characterized by a spindle shape and expression of markers, such as alpha smooth muscle actin, and are known to promote tumor growth (3). The mechanisms through which CAFs can contribute to tumorigenesis include secretion of growth factors and cytokines that activate proliferative signaling pathways in tumor cells (4). As the cells most responsible for secreting the proteins that comprise the extracellular matrix, the fibroblasts in CAFs have also been found to promote cancer growth through the creation of a cancer-promoting tissue microenvironment (4). Further, CAFs can enhance tumor angiogenesis by secreting cytokines that recruit endothelial cells that form tumor vasculature (5). Consistent with these findings, higher levels of CAFs are associated with larger tumors and shorter survival time (6).

Previous studies have hypothesized that fibroblasts can affect the metabolism of tumor cells. One model that has been put forward is that CAFs secrete metabolites that are absorbed and used as fuel by cancer cells (7). In support of this model, expression of MCT4, a transporter associated with lactate efflux, has been detected on the surface of cancer-associated fibroblasts, while MCT1, a lactate receptor associated with lactate uptake, has been observed on the surface of cancer cells (8). Extracellular vesicles are becoming increasing recognized as a mechanism of intercellular communication through the transfer of macromolecules including RNA, DNA, protein, and lipids (9). Exosomes have been shown to mediate cancer cell-CAF communication. Chronic lymphocytic leukemia-derived exosomes, for instance, have been found to reprogram surrounding cells to take on a CAF-like phenotype (10).

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Exosomes have also been linked to the metabolism of cancer cells. Breast cancer cells have been found to secrete exosomes containing the microRNA miR-122, which reduces glucose uptake by surrounding cells. The cancer cells, with increased glucose available, are then better able to metastasize (11). Exosomes can also be transmitted from cancer-associated fibroblasts to cancer cells. CAF-derived exosomes have been reported to provide metabolites that cancer cells can use as fuel, and to inhibit mitochondrial oxidative phosphorylation in the cancer cells (12).

Yan *et al.* now extend this body of work by reporting that cancer cells and CAFs functionally influence each other through a previously unrecognized mechanism of MYC- and exosome-dependent metabolic rewiring. They show that MYC activity in breast cancer cells leads to the secretion of *miR-105*-containing exosomes. When taken up by surrounding CAFs, exosomal *miR-105* activates a MYC-driven metabolic programme that fuels cancer cell growth by releasing key metabolites in the tumour microenvironment (13).

The authors observed that when taken up by patient-derived CAFs, extracellular vesicles derived from breast cancer cells induced a gene expression programme related to MYC activation. They linked this observation to the downregulation of MXI1, a known antagonist of MYC transcriptional activity. Reduced MXI1 levels in CAFs resulted in high MYC activity and increased expression of known MYC target genes, including the glycolytic enzymes hexokinase and lactate dehydrogenase. The authors went on to show that MXI1 was directly repressed by *miR-105*, a microRNA detected at high levels in exosomes derived from breast cancer cells. Interestingly, they found that *miR-105* was itself induced by MYC in cancer cells, indicating the existence of a MYC-based regulatory axis between cancer cells and CAFs through the action of exosomal *miR-105*.

The authors provided multiple lines of evidence to support these observations. They demonstrated that a sequence in the 3’ UTR of the MXI1 gene was targeted by *miR-105*. Overexpression of a MXI1 mutant lacking the 3’ UTR prevented MYC activation in CAFs. Taken together, high levels of MYC in cancer cells upregulated MYC activity in the surrounding CAFs through the activity of exosome-transported *miR-105* on MXI1.

Yan et al. then sought to understand whether MYC activity in CAFs promotes tumor growth. Given the known roles for many MYC targets in regulating cancer metabolism (14), the authors decided to investigate how MYC affects metabolism in CAFs. Their studies revealed that *miR-105*-reprogrammed CAFs show an improved ability to metabolize glucose or glutamine. When cultured with labeled glucose or glutamine, CAFs pre-incubated with extracellular vesicles generated elevated levels of intracellular and secreted metabolites, such as lactate and acetate, which can be consumed by adjacent cancer cells. Gene expression profiling indicated an upregulation of genes responsible for glycolysis, glutaminolysis and metabolite transport in *miR-105*-reprogrammed fibroblasts, which might underlie the altered metabolism. The authors concluded that *miR-105*-mediated reprogramming of CAFs results in “metabolic plasticity” that facilitates efficient consumption of either glucose or glutamine, for instance, if the other is absent, and supplies adjacent cells with nutrients.

In addition, reprogrammed CAFs also became capable of consuming metabolites that were not part of their usual energy sources. For instance, they consumed increased amounts of lactate if present at high levels, which normalized the extracellular pH and provided a nutrient source from which the fibroblasts could generate acetate, amino acids and UMP. Intriguingly, *miR-105*-reprogrammed CAFs also adapted to survive under unfavourable conditions that included glutamine depletion and high ammonium levels, indicating their improved ability to convert inorganic ammonium into amino acids and to secrete glutamate. Interestingly, breast cancer cells also showed increased survival when co-cultured with miR-105-reprogrammed CAFs in glutamine-depleted and high ammonium conditions. To provide further in vivo evidence, *miR-105*-expressing breast cancer cells were mixed with CAFs expressing *anti-miR-105* or a control sequence, and introduced into immuno-compromised mice. When compared with CAFs expressing a control miRNA, anti-miR-105-expressing CAFs failed to promote growth of co-transplanted tumor cells. Tumors formed from anti-miR-105-expressing CAFs had an impaired ability to metabolize injected labeled glucose or glutamine.

Finally, the authors investigated whether a similar network of MYC activity exists in human breast cancers. In line with their hypothesis that MYC-induced *miR-105* in cancer cells promotes MYC signalling in surrounding CAFs, they discovered a strong positive association between MYC activity in tumor cells and the stroma. Further, a high level of stromal *miR-105* was correlated with low levels of MXI1 and high levels of nuclear MYC.

Previous studies have demonstrated several mechanisms by which cancer cells co-opt surrounding fibroblasts, such as through secretion of transforming growth factor-β, epidermal growth factor and C-X-C motif chemokine ligand 12 (15). The MYC-*miR-105*-MXI1-MYC pathway proposed by Yan et al. provides an interesting and previously unappreciated mechanism for CAF reprogramming mediated by an exosomal miRNA that acts to reduce expression of target gene MXI1 and activate MYC activity in neighboring CAFs.

CAFs are known to promote tumor growth through multiple mechanisms including secretion of growth promoting molecules and modulation of the mechanical properties of the extracellular matrix (4). In the present study, Yan et al. identified a role for CAFs in providing nutrients to cancer cells and endowing them with the metabolic flexibility to adapt to adverse metabolic conditions (13). Based on this unique supportive function, CAFs allowed tumor cells to survive and thrive under conditions of low or high glucose, low or high glutamine and low or high pH. As tumours progress and expand during uncontrolled proliferation, nutrients are typically depleted and pH levels altered. Yan et al. now describe another strategy that allows cancer cells to re-engineer and enlist surrounding cells to alter their microenvironment to help them survive and even thrive under these hostile conditions.

As a whole, these findings open up several exciting questions. For instance, it would be interesting to know whether the phenomenon of correlated MYC activity in CAFs and tumor cells is also applicable to other oncogenes. Might it be possible to modulate adjacent cells by the activation of other oncogenes or inactivation of other tumor suppressors in cancer cells? The general applicability of the proposed crosstalk between tumor cells and CAFs through

exosomal miRNAs would be a valuable topic for further study. Are other miRNAs transported through exosomes also important for CAF reprogramming? Further questions focus on the metabolic reprogramming achieved, for instance, do CAFs in human tumors detoxify high levels of lactic acid or ammonium or other metabolic byproducts to facilitate the survival of cancer cells? The current work does not provide insights on whether other types of stromal cells in the tumor microenvironment or normal tissues, in addition to CAFs, might be affected by the exosomes studied. Currently the translational implications of these findings are unclear, but it would be interesting to know whether sufficient amounts of exosomal microRNAs could be applied to affect stromal cells in human tumors. Alternatively, would a strategy to prevent MYC activation in surrounding CAFs in vivo provide an effective therapeutic strategy to control tumor growth?

In conclusion, this work by Yan et al. expands our current knowledge on contributions of CAFs to the microenvironment and cancer survival and unlocks many exciting avenues for further in-depth investigation.

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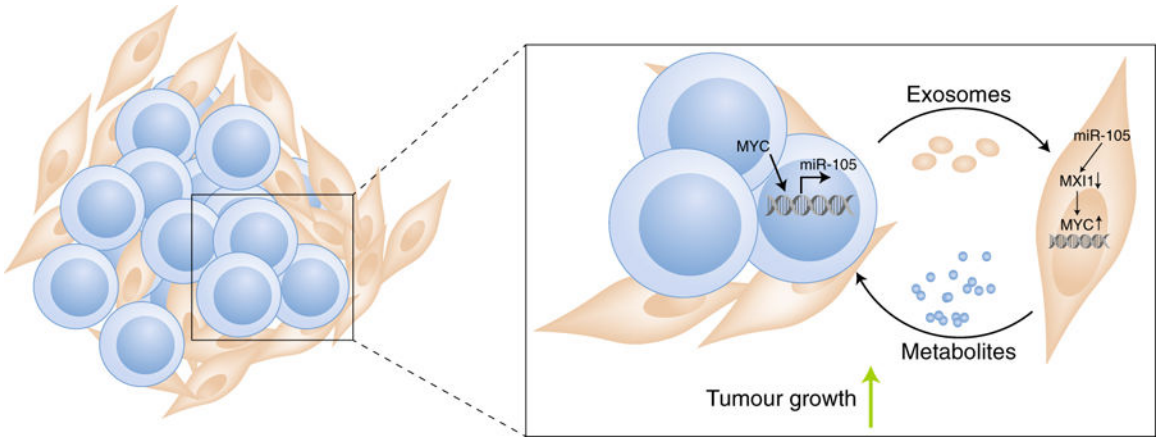

Figure 1.

Schematic model of the MYC-dependent metabolic rewiring of CAFs and tumour cells through exosomal *miR-105*. MYC activity in cancer cells results in increased expression of the microRNA miR-105, which is then transported via exosomes from cancer cells to surrounding CAFs. *miR-105* reduces transcript levels of MXI1, an inhibitor of MYC activity, thereby increasing MYC-dependent gene expression in CAFs. Among the induced MYC target genes are metabolic enzymes, leading to an increased metabolic flexibility of the CAFs and the release of metabolites in the tumour microenvironment that promote tumour growth.