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PROSTATE CANCER

Sending a signal through oncosomes

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The first data showing that large oncosomes — a type of extracellular vesicle — have roles in cancer cell intercellular communication and contribute to the reprogramming of normal prostate cells have been published in *Cancer Research*. These results could provide new targets for cancer therapy.

Large oncosomes are abnormally large extracellular vesicles formed by the pinching off of membrane blebs on prostate cancer cells. Minciacchi *et al.* hypothesized that these oncosomes could facilitate intercellular communication.

Large oncosomes were internalized by a variety of cells *in vitro*, including normal-associated prostatic fibroblasts, DU145 cells and LNCaP cells. Oncosome uptake was inhibited by refrigeration and inhibition of phagocytosis. Internalization of large oncosomes caused tube branching and induced a fibroblast phenotype. Exposure to conditioned media from large-oncosome-treated cells induced tube branching *in vitro*.

Treatment with large oncosomes induced expression of IL-6, MMP9, α-SMA and MYC (also known as c-MYC) in normal-associated prostatic fibroblasts, with MYC being highly activated according to RNA sequencing; however, MYC was not identified in large oncosomes themselves. These cells also had increased expression of FGF2, GLS and LDH — known transcription factors of MYC. Genetic silencing and small molecule inhibition of MYC blocked oncosome-induced MYC activity. Furthermore, blocking the uptake of large oncosomes by cells reduced MYC activation.

In vivo, MYC overexpression in primary prostatic fibroblasts in grafted tissue recombinants placed in the subrenal capsule of mice resulted in hyperplasia of adjacent prostatic epithelium. Moreover, cell-line-derived xenografts pretreated with large oncosomes grew significantly more than untreated xenografts. This effect was negated by blocking oncosome uptake or inhibiting MYC.

The investigators observed that large oncosomes derived from patients with metastatic prostate cancer and prostate cancer cell lines contained significantly more phosphorylated AKT1 than exosomes (nano-sized extracellular vesicles) and MYC activation in the stroma requires AKT1 activity. Activated AKT1 was readily precipitated from large oncosomes; furthermore, large oncosomes induced AKT1 phosphorylation in normal-associated prostatic fibroblasts. AKT1 inhibition in large oncosomes caused reduced MYC activity, α-SMA expression and tube branching in these cells.

These results provide evidence that intercellular communication might occur through a tumour-specific discrete population of extracellular vesicles, which induce specific signalling pathways in the cells that take them up. This novel mechanism could be a target for future therapies for prostate cancer.

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> “large oncosomes induced AKT1 phosphorylation in normal-associated prostatic fibroblasts”

ORIGINAL ARTICLE Minciacchi, V. R. *et al.* MYC mediates large oncosome-induced fibroblast reprogramming in prostate cancer. *Cancer Res.* http://dx.doi.org/10.1158/0008-5472.CAN-16-2942 (2017)