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Investigating a new leptin-induced molecular mechanism that links obesity and oestrogen receptor-negative breast cancer

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Background: Obesity is a known risk factor for breast cancer. Sphingosine kinase 1 (SK1) is an oncogenic lipid kinase that is overexpressed in breast tumours and linked with poor prognosis, however its role in obesity-driven breast cancer was never elucidated.

Materials and Methods: Human primary and secondary breast cancer tissues were analysed for SK1 and leptin receptor expression using quantitative real time polymerase chain reaction (qRT-PCR) assay. Leptin-induced signalling was analysed in human oestrogen receptor positive and negative breast cancer cells using Western blotting, qRT-PCR and radiolabelling assays.

Results: Our findings show for the first time that human primary breast tumours and associated lymph node metastases exhibit a strong correlation between SK1 and leptin receptor expression (Pearson R=0.78 and R=0.77, respectively, $p<0.001$). Both of these genes are elevated in metastases of oestrogen receptor (ER)-negative patients and show a significant increase in patients with higher body mass index (BMI). Leptin induces SK1 expression and activation in ER-negative breast cancer cell lines MDAMB-231 and BT-549, but not in ER-positive cell lines. Pharmacological inhibition and gene knockdown showed that leptin-induced SK1 activity and expression are mediated by activation of extracellular signal-regulated kinases 1/2 (ERK1/2) and Src family kinases (SFKs) pathways, but not by the major pathways downstream of leptin receptor (LEPR) - janus kinase 2 (JAK2) and signal transducer and activator of transcription 3 (STAT3). Src-homology 2 domain-containing phosphatase 2 (SHP2) appeared to be key to SK1 activation, and may function as an adaptor protein between SFKs and LEPR. Our data show that leptin-induced STAT3 phosphorylation was further dependent on SK1 through SK1-dependent release of IL-6 and crossactivation of gp130. Importantly, leptin-induced breast cancer cell proliferation was abrogated by SK1 specific small interfering RNA (siRNA).

Conclusions: Overall, our findings demonstrate a novel SFK/ERK1/2-mediated pathway that links, leptinsignalling and expression of oncogenic enzyme SK1 in breast tumours and suggest the potential significance of this pathway in ER-negative breast cancer.

Notes: