AB069. SOH22ABS209. The epitranscriptomic landscape in estrogen receptor (ER)-positive breast cancer disease progression

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Background: Breast cancer is a highly heterogeneous and progressive disease and is a major cause of mortality worldwide. Significant clinical advances require detailed understanding of tumour cell adaptability and progression to metastases. To understand the role of the epitranscriptome in tumorigenesis we mapped dynamic global Ribonucleic acid (RNA) epitranscriptomic in progressive estrogen receptor (ER)-positive disease.

Methods: To define the m6A methyl landscape, MeRIP-sequencing was performed in models of breast cancer disease progression. The global proteome was mapped using mass spectrometry, allowing validation of the functional output of methyl modifications. Using a large patient cohort (n=920) the effect of key RNA-methyl machinery, fat mass and obesity-associated protein (FTO), ALKBH5, METTL3 and METTL14 on overall survival and progression-free survival was assessed. Functional assays and PDX-*ex-vivo* and organoid models were used to investigate the translational efficacy of targeting key RNA-methyl modulators in the management of advanced breast cancer.

Results: Global gains in m6A methylation were observed with disease progression. Integration of the methylome and proteome revealed a strong correlation of perturbations in stem cell differentiation pathways. Notably RNA demethylator FTO, mediates the expression of stem cell genes KLF4, SOX2 and SOX4. FTO associated with poor overall (P=0.04) and progression-free survival (P=0.02) in breast cancer patients. Pharmacological inhibition of FTO reduced stem cell gene expression and tumour cell growth in patient brain metastatic models.

Conclusions: We provide evidence that dysregulated m6A modifications are a pertinent feature of progressive disease. We report that FTO an RNA methyl 'eraser' can drive tumorigenesis through modulation of stem cell differentiation. Targeting FTO represents a promising novel approach to managing advanced breast cancer.

Keywords: Breast cancer; epitranscriptome; fat mass and obesity-associated protein (FTO); Ribonucleic acid methylation (RNA methylation); stem cell

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