Coordinated regulation of Nuclear Envelope integrity and STING trafficking by miR-30d suppresses innate immunity in Breast Cancer

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Tumour cells actively remodel the surrounding microenvironment to generate an immune-excluded niche that supports sustained tumour progression and limits therapeutic efficacy. We previously showed that cellular stress and mutant-p53–driven induction of the onco-miRNA miR-30d in breast cancer (BC) promotes a pro-tumorigenic secretome that reshapes the tumour microenvironment (TME). Through integrated transcriptomic and mechanistic analyses, we now identify miR-30d as a central suppressor of cytosolic DNA sensing and type I interferon (IFN-I) signalling. miR-30d attenuates the cGAS–STING pathway via two distinct mechanisms. Upstream, it preserves nuclear envelope integrity through the LATS2–YAP–Lamin B1 regulatory module, thereby reducing nuclear rupture, genomic instability, and cytosolic DNA leakage that would otherwise activate cGAS. In parallel, miR-30d impairs STING trafficking from the endoplasmic reticulum to the Golgi, limiting TBK1 activation and downstream IFN-I propagation. Pharmacological or genetic inhibition of miR-30d restores both cGAS activation and STING transit, eliciting a robust IFN-I response in BC cells, without affecting non-transformed breast epithelial cells and re-engages antitumour immune surveillance in preclinical models. Consistent with these mechanistic insights, analyses of BC patient datasets reveal that elevated miR-30d activity inversely correlates with transcriptional signatures of innate antitumour immunity, supporting its role in establishing an immune-cold, poorly infiltrated TME. Functionally, miR-30d inhibition using a specific decoy sponge and locked nucleic acid suppresses tumour growth and enhances responsiveness to immune checkpoint blockade, underscoring its therapeutic relevance. These findings position miR-30d as a key regulator of a nuclear envelope–Golgi signalling axis that restrains innate immune surveillance in breast cancer. Targeting miR-30d may offer a promising strategy to overcome immune evasion and potentiate immunotherapy efficacy