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The potential of miR-630, an IGF1R regulator, as a predictive biomarker for HER2-targeted drugs.

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Background: Innate or acquired resistance to current HER-targeting drugs indicates that their use for HER2-overexpressing breast cancer (BC) treatment may be compromised. miRNAs may have potential as diagnostic, prognostic and predictive biomarkers for treatment response, as well as therapeutic targets and replacement therapies. We aimed to investigate miR-630 as a predictive biomarker for response to a range of HER-drugs and as a potential target for increasing sensitivity to the same. **Methods:** Following global miRNA profiling using taqman low density arrays, the reduced expression of miR-630 in cells and corresponding conditioned medium (CM) of HER2-positive BC cell lines with acquired/innate lapatinib (L) resistance (SKBR3-LR, HCC1954-LR, MDA-MB-453) was confirmed by qPCR. miR-630 mimics and inhibitors were used to assess cell response to current (L, trastuzumab (T)) and emerging (neratinib (N), afatinib (A)) HER-targeting drugs. Targetscan prediction software and immunoblotting were used to determine miR-630 regulated proteins. **Results:** miR-630 levels were significantly decreased in cells and CM with acquired lapatinib resistance compared to their age-matched controls. Decreased miR-630 was also observed for innately resistant MDA-MB-453 compared to innately sensitive SKBR3. Administration of miR-630 mimic significantly sensitised resistant cells to all 4 drugs tested. Specifically, miR-630 mimic increased the anti-proliferative effects of L by 31% (SKBR3-LR), 9% (HCC1954-LR) and 9% (MDA-MB-453). Similarly, miR-630 mimic improved the efficacy of T (11-35%), N (4-17%) and A (9-25%); (range for different cell lines). Inhibition of miR-630 in sensitive parent cells induced an insensitive/resistant phenotype, significantly reducing

the efficacy of all 4 drugs tested. Interestingly, miR-630 also significantly regulates cell motility, invasion and *anoikis* resistance implicating this miRNA in overall cell aggressiveness.

Conclusions: This data suggests a potential role for miR-630 as a predictive biomarker for HER-targeting drugs as well as an additional therapeutic target for HER2-overexpressing BC.

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