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Douglas, R., Stevenson, L., Santos, R., Cairns, L., McCabe, N., Kennedy, R., Blayney, J., & Turkington, R. (2019). Targeting Survivin to overcome cisplatin resistance in oesophageal adenocarcinoma. *Journal of Clinical Oncology*.

Published in:
Journal of Clinical Oncology

Document Version:
Early version, also known as pre-print

Queen's University Belfast - Research Portal:
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Targeting Survivin to overcome cisplatin resistance in oesophageal adenocarcinoma.

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Background:

The incidence of Oesophageal Adenocarcinoma (OAC) has risen in the western world but response rates to chemotherapy are low and survival is poor. Increased molecular understanding is needed to develop novel treatment.

Methods:

Transcriptional profiling of 274 treatment naïve OAC biopsies was performed using the Almac Diagnostics Xcel array™. All patients received platinum-based neo-adjuvant chemotherapy prior to surgical resection at four United Kingdom centres between 2004-2012. Semi-supervised clustering was performed followed by functional enrichment using DAVID. Cluster membership was assessed for independence of prognostic factors using Cox proportional hazards. SiRNA screening in OE33 cells was performed for cell viability using MTT. The role of candidate genes were validated through siRNA knock down using western blotting and PCR. Treatment with the survivin inhibitor, YM155 in OAC cell lines was also assessed.

Results:

Unsupervised hierarchical clustering separated the patients into two groups with significant RFS [HR= 0.54 (0.29-0.99), p= 0.05] and OS [HR= 0.52 (0.28-0.96), p= 0.04]. There were significant associations between the clusters and both nodal and TNM downstaging but not with pathological response. The PI3K-AKT, p53, tight junction and HIF-1 signalling pathways are upregulated in the poor prognostic group.

Eighty-four genes were selected and taken forward into a genomic siRNA screen. Twenty-seven genes showed a significant reduction in viability following siRNA-mediated knockdown and verification with a further two siRNAs resulted in twelve candidate genes. Finally, target knockdown in seven OAC cell lines resulted in four interrelated hits which are BIRC5, JAK1, OSMR and SLC2A1.

Knock down of BIRC5 (Survivin) induced apoptosis, as evidenced by PARP cleavage, in both the parental OE33 and cisplatin-resistant OE33CDDPR cell lines. Silencing of OSMR leads to reduction of pAKT(S473) and increased in PARP cleavage in a time course manner. YM155, a survivin inhibitor is shown to have IC30 at nanomolar concentrations across the panel. Further work is ongoing to validate knock down at the gene level and also to study the role of the OSMR/JAK/STAT3 pathway in OAC.

Conclusions:

We have performed molecular stratification of a large dataset and defined a poor prognostic group of OAC patients. We identified Survivin (BIRC5) as a mediator of cisplatin resistance in OAC and a potential novel drug target. Further pre-clinical and clinical work to assess the benefit of survivin inhibition in patients with OAC should be considered.