# Hyaluronic Acid in High-Grade Serous Ovarian Cancer Plasticity

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High-grade serous ovarian cancer (HGSOC) is the deadliest epithelial ovarian cancer, usually diagnosed at advanced stages with peritoneal metastases and malignant ascites. In the HGSOC microenvironment, hyaluronic acid (HA) drives extracellular matrix remodelling and metastasis. HA is synthesized by HAS1–3, with HAS2 producing high-molecular-weight HA (HMW-HA) linked to tumour progression.
Altered HA promotes an immunosuppressive niche facilitating peritoneal dissemination. KMplot analysis showed that patients with high HAS2 expression, optimal debulking (< 1 cm² residual), and grade 1–2 tumours had higher recurrence risk (HR=2.32), supporting HMW-HA's role in relapse.

To investigate the contribution of HMW-HA to HGSOC plasticity, HAS2 was overexpressed in a murine HGSOC cell line (HGS2). HAS2 overexpression promoted microsatellite formation around spheroids and enhanced survival under 3D non-adherent conditions, mimicking malignant ascites. Treatment with recombinant hyaluronidase or 4-methylumbelliferone (4-MU) prevented microsatellite formation without disrupting spheroid cores, indicating a specific role for HMW-HA in tumour cell plasticity.

RNA-seq analysis of HAS2-overexpressing cells revealed enrichment of hypoxia-related gene ontology terms. Functionally, these cells exhibited increased ATP-linked respiration and neutral lipid accumulation. Mechanical compression assays further demonstrated greater deformability and reduced compactness in HGS2-HAS2 spheroids, consistent with enhanced mechanical compliance.

In vivo, HAS2-expressing cells induced earlier ascites formation. Based on these findings, we are currently performing a drug repurposing screen using the Prestwick Chemical Library to identify compounds capable of targeting HA-driven plasticity.

Collectively, these results identify HMW-HA as a driver of metabolic adaptation and aggressiveness in HGSOC, highlighting HA metabolism as a promising therapeutic vulnerability.