Hedgehog signalling pathway activity in high-grade serous ovarian carcinoma

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Introduction

High-grade serous (ovarian) carcinoma (HGSC) is the most lethal gynaecological malignancy with a 5-year survival rate of approximately 30%[1]. Knowledge on the cellular processes in carcinogenesis, such as signal transduction pathways (STPs), is needed for the development of targeted therapies[2]. One such STP is the hedgehog (HH) pathway and previous research yielded contradictory results on HH activity in HGSC[3]. As most HGSC are thought to arise from Fallopian tube epithelium (FTE), **the aim of our study** was to determine the *functional* HH activity in HGSC and Fallopian tube stem cells (FTSC) compared to normal FTE, in order to provide new insights in the HGSC cell type of origin and the potential use of HH targeted therapies.

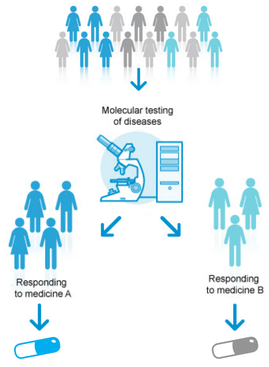


Figure 1. Overview of the personalized cancer treatment with targeted therapy.

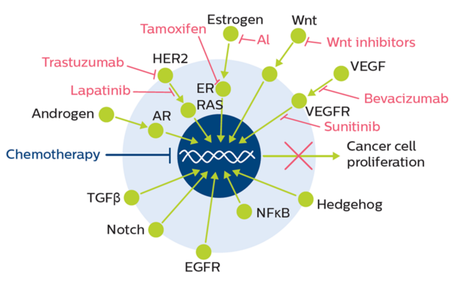


Figure 2. Overview of important signal transduction pathways that drive tumour growth and some therapeutic options.

Methods

We used a computational diagnostic approach, signal transduction pathway activation (STA) analysis, enabling quantitative measurements of the *functional* pathway activity using Bayesian networks that look at mRNA levels of pathway target genes resulting from activation[4]. STA-analysis was performed on publicly available Affymetrix data (GSE28044, GSE9891 and GSE69428) containing microdissected **normal FTE (*n*=22), HGSC (*n*=150) and cultured FTSC (*n*=2)**[5-7].

Methods

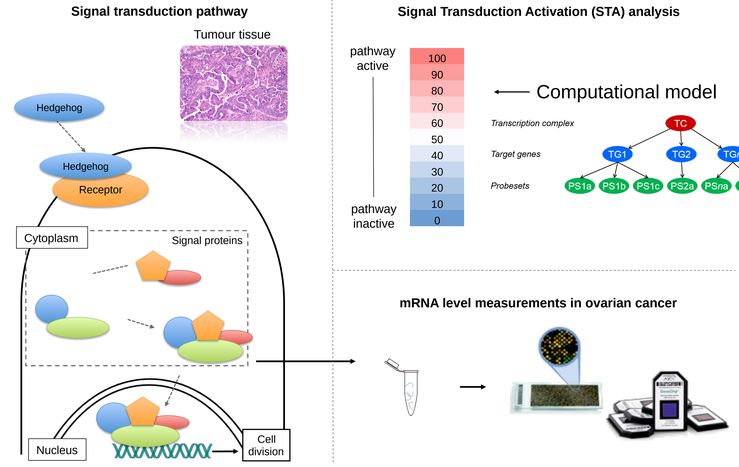


Figure 3. Schematic overview of the hedgehog (HH) pathway (left) and analysis method (right).

Results

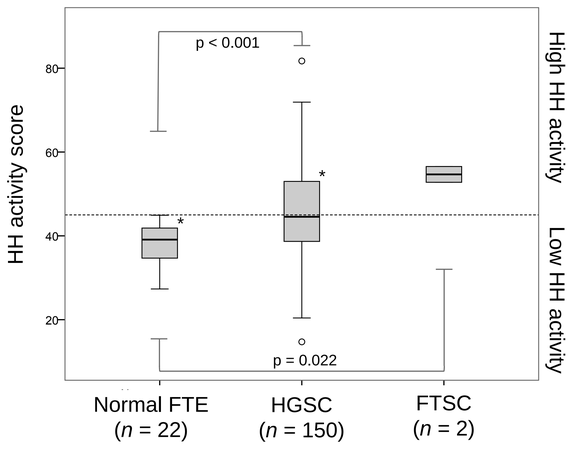
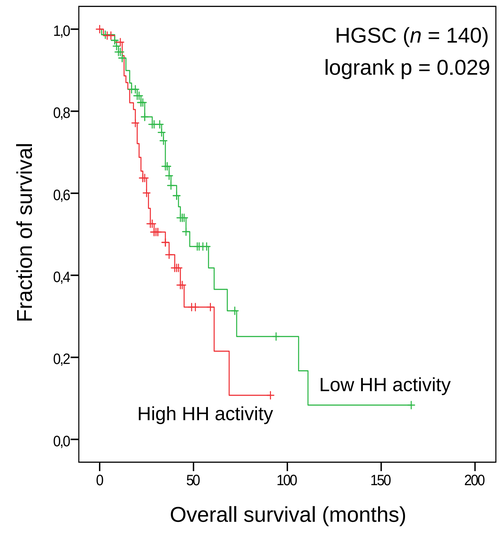


Figure 4. Hedgehog (HH) pathway activity scores measured with STA-analysis in normal Fallopian tube epithelium (FTE), high-grade serous carcinoma (HGSC) and Fallopian tube stem cells (FTSC). Data was statistically analysed with Mann-Whitney U tests. *Functional* HH activity was higher in HGSC ($p < 0.001$) and FTSC ($p = 0.022$) compared to normal FTE. *Thirty samples showed a degree of RNA degradation.

Results

We demonstrated **higher *functional* HH activity in HGSC** ($p < 0.001$) and FTSC ($p = 0.022$) compared to normal FTE (Figure 4). HH activity in HGSC and FTSC were comparable, supporting the hypothesis of FTSC as the cell type of origin of HGSC. This is in agreement with earlier findings of Fallopian tube stem-like cells in cancerous lesions in the distal fimbriae[8]. We considered 47% of HGSC as highly HH active and **correlated this to poor overall survival** ($p = 0.029$) (Figure 5).

Figure 5. Survival plot illustrating high (HH score > 45) and low (HH score ≤ 45) HH activity in 138 high-grade serous carcinomas (HGSC) with overall survival (months) ($p = 0.029$).



Conclusions

With the use of STA-analysis we showed significant higher *functional* HH activity in HGSC and FTSC compared to normal FTE, suggesting that the HH STP has a tumour-promoting role in HGSC. We indicated 47% of the HGSC as highly HH active and correlated this to poor survival. **We suggest that the HH active subpopulation of HGSC might be of interest for HH targeted therapies**.

References
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Project in collaboration with:
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