

Measuring functional PI3K and NFκB pathway activity to distinguish between short-term and long-term disease-free survivors of high grade serous ovarian cancer

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Introduction

- Disease Free Survival (DFS) varies greatly among women with High-Grade Serous Ovarian Cancer (HGSC) despite comparable clinicopathological features and treatment
- The underlying mechanism might be previously unknown differences in activity of tumour-driving signal transduction pathways
- Signal Transduction pathway Activity assays have recently been developed^{a,b}
- We aim to explore Signal Transduction pathway Activity (STA) in HGSC patients in relation to DFS

Objective

Differentiate between short-term and long-term disease free survivors of HGSC based on signal transduction pathway activation

Material and Methods

Datasets

We used a publicly available dataset of primary HGSC samples with clinical annotations (data accessible at NCBI GEO database, accession GSE9891)

- HGSC samples from GSE9891 were analysed with STA-analysis which infers pathway activity scores from measurements of mRNA levels of target genes of the transcription factor associated with the signalling pathway
 - Note: activity of the FOXO transcription factor is inversely related to PI3K pathway activity^c
- Based on a preliminary study, we hypothesize that low PI3K with high NFKB pathway activity may be associated with improved clinical outcome
- We clustered samples with repeated k-means clustering based on NFKB and PI3K-FOXO pathway activity and examined both DFS and overall survival (OS)

Results

- GSE9891 contained 140 primary HGSC samples with clinical annotations. Repeated k-means clustering based on PI3K-FOXO and NFKB activity resulted in two clusters:
 - A cluster with high FOXO (low PI3K pathway activity) and high NFKB pathway activity (n=72)
 - A cluster with low FOXO (high PI3K pathway activity) and low NFKB pathway activity (n=68)
- For the low PI3K and high NFKB pathway activity cluster, both DFS (p=0.018; figure 1) and OS (p=0.012; figure 2) were more favourable

Results

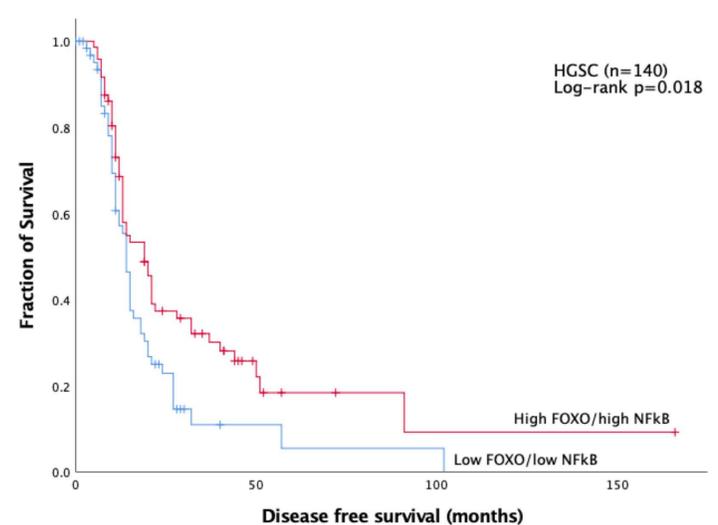


Figure 1.

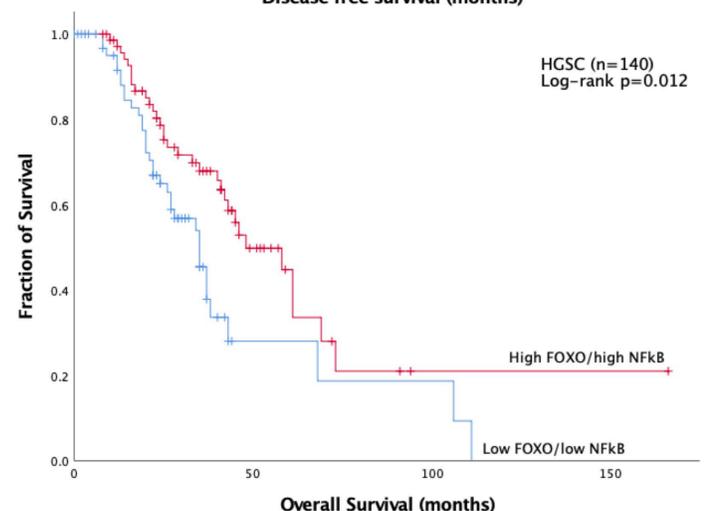


Figure 2.

Discussion and Conclusion

- Low PI3K and high NFKB pathway activity were associated with a more favourable prognosis
- High PI3K and low NFKB pathway activity were associated with a less favourable prognosis

Conclusion

We identified two subgroups in HGSC with a difference in DFS and OS based on NFKB and PI3K pathway activity in STA analysis. Activity of the PI3K pathway as measured by STA is associated with worse prognosis, and might provide a novel treatment target

References:

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- b. Stolpe A van de, et al., Sci Rep. 2019;9:1603
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