Abstract

Background: There is a critical unmet need for targeted therapies in ovarian cancer, especially high-grade serous ovarian cancer (HGSOC), where 70% of patients present with late-stage disease associated with transmucosal invasion and residual tumor burden. Currently available treatment options are primarily based on chemotherapy and targeted therapies, leading to high relapse rates and poor overall survival. Therefore, there is a need for new drug targets and more rational strategies to treat ovarian cancer.

Methods and materials: To identify novel enhancer-defined subtypes of 101 primary ovarian cancer samples from 7 ovarian cancer subtypes with a focus on HGSOC, 29 cell line models, 3 PDXs, and 8 non-can-cerous samples, we analyzed the enhancer activity of each sample through the construction of a super-enhancer landscape (SE map). We used matrix factorization methods to reveal novel subgroups of ovarian cancer patients and provide new insights into their clinical characteristics.

Results: Through a computational deconvolution of enhancer maps, we identified novel enhancer-defined subtypes of ovarian cancer by clustering enhancer activity across all samples including matched primary patient samples through H3K27Ac ChIP-seq signal. We then focused on the landscape of enhancer activity with high-confidence ovarian cancer mutations. Each cluster was associated with a unique enhancer signature. This novel clustering approach revealed a distinct enhancer landscape in ovarian cancer, including an SE-defined trajectory to the H4 pathway gene Cyclin G1. Furthermore, several cluster-specific SEs were defined, and enrichments were linked to specific biological pathways relevant to ovarian cancer.

Conclusions: Together, our results comprise the largest ovarian cancer enhancer mapping effort to date, and demonstrate that an integrated analysis of enhancers, transcription factors, and gene expression together can yield additional insights into the clinicopathological characteristics of ovarian cancer patients. These findings can be used to select cell models that best recapitulate the enhancer landscapes and biological pathways of ovarian cancer. In addition, understanding the role of enhancers in ovarian cancer can inform the development of targeted therapies and guide clinical decision-making.

Method - Cell SEs, NMF, & cluster

Defining pairs of cell SEs across normal and tumor samples

Novel ovarian cancer patient subgroup identification through NMF

Differential enhancer activity between tumor and normal

Novel ovarian cancer patient subgroup identification through NMF

Differential super-enhancer landscapes across samples identifies normal- and tumor-specific transcriptional circuitry

Conclusions

We have constructed the largest H3K27Ac ChIP-seq database in ovarian cancer and related normal tissue data to date, with the express purpose of identifying novel enhancer activity. We complemented our ChIP-seq data with RNA-seq data to further validate our novel enhancer-defined subtypes. Our results demonstrated that enhancer-defined ovarian cancer subtypes and tumors are distinct in gene expression, as well as cell line models and PDXs. Our findings suggest that enhancer-defined subtypes are linked to known oncogenes such as MYC, and that these subtypes are associated with the downstream transcriptional regulation of known pathways. We identified several novel enhancer-defined subtypes, including granulosa cell and yolk sac, that are not linked to known oncogenes or pathways. Our findings suggest that enhancer-defined subtypes may provide new insights into the molecular biology of ovarian cancer and may guide the development of targeted therapies.