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Perspective

Proteogenomic Mapping of Treatment Resistance in Ovarian Carcinoma

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DESCRIPTION

Ovarian carcinoma remains one of the deadliest gynecologic malignancies worldwide, largely due to late diagnosis and the development of treatment resistance. Despite initial responsiveness to platinum-based chemotherapy and targeted therapies such as Poly (ADP-Ribose) Polymerases (PARP) inhibitors, a substantial fraction of patients ultimately experience relapse, often characterized by multidrug resistance. Understanding the molecular basis of this resistance is crucial for improving therapeutic outcomes. Recent advances in proteogenomics, which integrate proteomic and genomic data, have enabled high-resolution mapping of the molecular landscape of ovarian carcinoma, revealing novel mechanisms underlying therapy resistance.

Proteogenomics combines next-generation sequencing with quantitative mass spectrometry-based proteomics, providing simultaneous insights into DNA mutations, RNA expression, protein abundance, post-translational modifications, and signaling pathway activity. Unlike traditional genomic analyses that only capture static DNA alterations, proteogenomics captures functional outcomes at the protein level, including aberrant phosphorylation, acetylation, and ubiquitination events that directly influence cellular behavior. In ovarian carcinoma, this approach allows for the identification of molecular alterations driving chemoresistance, immune evasion, and metastatic progression.

One key mechanism of platinum resistance involves alterations in DNA damage repair pathways. High-grade serous ovarian carcinoma frequently harbors mutations in BRCA1/2, leading to Homologous Recombination Deficiency (HRD) and initial sensitivity to platinum compounds and PARP inhibitors. However, secondary mutations that restore BRCA function or alternative DNA repair mechanisms, such as Non-Homologous End Joining (NHEJ) and replication fork stabilization, confer resistance. Proteogenomic analyses have revealed that resistance is often accompanied by upregulation of proteins involved in DNA repair complexes, post-translational modification of key repair enzymes, and activation of compensatory signaling pathways.

Beyond DNA repair, alterations in signaling pathways governing cell survival, apoptosis, and metabolism contribute to treatment resistance. For example, phosphorylation of AKT or ERK may occur without corresponding mRNA overexpression, highlighting the importance of proteomic measurements. Metabolic rewiring, including enhanced glycolysis, oxidative phosphorylation, and lipid metabolism, has also been implicated in chemoresistance. Proteomic profiling captures these functional metabolic adaptations, revealing vulnerabilities that may be exploited therapeutically, such as inhibition of fatty acid synthesis or mitochondrial respiration.

The Tumor Microenvironment (TME) plays a critical role in ovarian carcinoma progression and resistance. Proteogenomic studies have demonstrated that resistant tumors often exhibit enriched stromal and immune signatures, including increased cancer-associated fibroblast activity, immunosuppressive cytokine secretion, and altered extracellular matrix remodeling. These microenvironmental factors can protect tumor cells from cytotoxic therapy, reduce immune surveillance, and promote metastasis. By integrating single-cell proteomics with genomic data, researchers can deconvolute TME contributions and identify actionable interactions between tumor cells and surrounding stroma or immune populations.

Importantly, proteogenomic mapping also provides insights into acquired resistance to targeted therapies, including PARP inhibitors and anti-angiogenic agents. For instance, upregulation of drug efflux pumps, activation of bypass signaling pathways, and post-translational modifications of target proteins can reduce drug efficacy. Identification of these alterations at the protein level allows for rational design of combination therapies to prevent or overcome resistance. In clinical settings, longitudinal proteogenomic profiling of tumor biopsies or minimally invasive liquid biopsies can monitor the emergence of resistance, enabling timely adaptation of therapeutic strategies.

Translational applications of proteogenomics in ovarian carcinoma are exemplified by the Clinical Proteomic Tumor Analysis Consortium (CPTAC) and other multi-institutional studies, which have characterized hundreds of high-grade serous ovarian tumors. Integrative analysis has identified novel biomarkers predictive of treatment response, including protein

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phosphorylation signatures associated with platinum sensitivity, immune checkpoint expression linked to immunotherapy potential, and metabolic proteins indicative of adaptive survival mechanisms. Such findings pave the way for personalized treatment strategies, moving beyond genomic profiling alone to incorporate dynamic functional insights at the protein level.

Looking forward, combination strategies leveraging proteogenomic insights hold promise for overcoming treatment resistance. Targeting DNA repair alterations in conjunction with metabolic or signaling vulnerabilities, modulating the tumor microenvironment, or combining cytotoxic therapy with immunotherapy can be rationally designed based on integrated proteogenomic maps. Moreover, advances in single-cell proteogenomics and spatial proteomics will enable mapping of heterogeneity at unprecedented resolution, identifying subpopulations responsible for resistance and relapse. Ultimately, these approaches aim to transform ovarian carcinoma management by providing actionable molecular insights to guide personalized therapy.

CONCLUSION

Proteogenomic mapping provides a comprehensive and functional view of the molecular landscape of ovarian carcinoma, revealing mechanisms underlying treatment resistance that cannot be captured by genomics alone. Integration of proteomic and genomic data has elucidated alterations in DNA repair, signaling pathways, metabolism, and the tumor microenvironment, highlighting potential therapeutic targets and predictive biomarkers. Continued refinement of proteogenomic approaches, combined with longitudinal and single-cell analyses, offers the potential to guide precision oncology, improve treatment outcomes, and ultimately reduce relapse in ovarian carcinoma patients.