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ON THE COVER
Hill and colleagues profiled DNA-repair activity to discover potential therapeutic vulnerabilities in 33 organoid cultures derived from 22 patients with high-grade serous ovarian cancer (HGSC). The majority of HGSC organoids exhibited functional homologous recombination (HR) and were insensitive to agents targeting HR defects including the PARP inhibitor olaparib. Although genetic alterations predicted to affect HR occurred more frequently, only 2 of 34 organoid cultures were olaparib-sensitive, indicating a lack of functional HR. Replication fork instability occurred in 61% of tested cultures and was linked to sensitivity to carboplatin, prexasertib, and VE-822. Combining prexasertib with carboplatin or gemcitabine could induce fork instability and replication stress in fork-stable lines. Together, these findings indicate that functional organoid profiling in concert with genomic analysis may aid the discovery of targetable DNA damage repair defects in patients with HGSC. For details, please see the article by Hill and colleagues on page 1404.