following are experimental avenues to be explored in search for such therapies.

**Targeting p53.** TNBC (basal-like and Claudin-low) with *dn* point mutations in p53 may be highly sensitive to drugs such as PRIMA-1 (p53 reactivation and induction of massive apoptosis), which refold and restore tumor suppressor function to many dn-p53 mutant proteins. The PRIMA-1 analogs, APR-246, is currently assessed in clinical trials.[119-121]

**Targeting Rb-deficiency.** As the Rb pathway is not druggable; i.e., restoration of RB1 function following mutation or deletion is not feasible, an alternative approach is to mimic its function as discussed in the previous section, or, conversely, to specifically kill Rb-deficient tumor cells. For example, the E2F1 promoter is deregulated in RB1 deficient tumor cells and this may offer a therapeutic window to kill cancer but not normal cells.[122] Indeed, Rb-deficient cells express high levels of pro-apoptotic factors and are prone to apoptosis;[60] therapeutic induction of E2F1, other pro-apoptotic factors or treatment with inducers of apoptosis may tilt the balance in favor of apoptotic cell death.[60,123] Alternatively, CDK inhibitors may be used to suppress cell cycle progression in the absence of pRb through activation of p107, p130 and other targets.[113]

**Chemotherapy.** The RB1-signature in BC includes proliferation-associated genes that are targets of conventional chemotherapy such as TOP2A (doxorubicin, etoposide), thymidylate synthetase (5-FU), ribonucleotide reductase M2 (hydroxyurea) and CDK1 (flavopiridol, staurosporine). This may explain the increased sensitivity of RB-deficient cells to chemotherapy.[113] Drugs that target Claudin-low BC may be different than those that target Basal-like BC; small-molecule drug screens may identify such subtype-specific cytotoxic drugs.

**Targeting cooperating oncogenic and metastatic networks.** BC cells typically contain over a dozen independent mutations that cooperate to induce transformation. Identification of oncogenic networks that cooperate with mutations in Rb and p53 would offer new therapeutic targets. Such cooperating mutations can be identified by genomic and transcriptome sequencing, copy number analysis or through functional screens using lentishRNA[124] and transposon-based mutagenesis.[125] For example, a recent RNAi screen for genes that can transform Tag immortalized human mammary epithelial cells identified PTPN12 tyrosine phosphatase as a tumor suppressor of TNBC.[126]

**Targeting EMT inducers.** Given the connection between EMT and TICs, inhibition of EMT inducers may target the TIC fraction. As noted, knockdown of Twist genes in several mesenchymal and non-mesenchymal tumor types induced cellular senescence,[40] suggesting that targeting this signaling network may be a promising approach.

**Targeting hypoxia and glycolysis.** Finally, while hypoxia and glycolysis confer metastatic advantage and protection from chemotherapy, they also represent vulnerabilities to drugs that inhibit these processes or their consequences such as Unfolded Protein Response (UPR) and Autophagy. Given the effect of Rb loss on these processes,[127] Claudin-low and Basal-like BC may be particularly sensitive to such inhibitors.

Additional therapeutic strategies including drugs currently evaluated for the treatment of TNBC such as PARP and EGFR inhibitors should also be explored. Combination therapy toward the above targets will increase specificity, lessen side effects and reduce the likelihood that resistant variants could emerge, thereby preventing relapse.

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