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BRCA associated pancreatic cancer & other DNA repair deficiencies

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Pancreatic ductal adenocarcinoma (PDAC) continues to pose a challenge globally and is expected to represent the second most common cause of cancer deaths in the next two decades. Familial clustering is found in about 10-15% of PDAC cases (FPC) with an apparent autosomal dominant pattern of genetic transmission, suggestive of an inherited cancer syndrome. An estimated 5% of FPC cases have DNA repair pathway aberrations. *BRCA1* and *BRCA2* deficient tumors, particularly in *BRCA1/BRCA2* germline mutation carriers, have a distinct clinical outcome and responsiveness to cisplatin-based therapy. PARPi may offer therapeutic promise in these cases and a phase III clinical trial is currently underway. Another familial subset resembles the BRCA- mutant clinical phenotype (displaying sensitivity to cisplatin therapy and improved prognosis) and maybe referred to as having DNA repair deficiencies (DDR), although their underlying genetic mutation is undefined. Recent whole genome sequencing studies have indicated that a subset of PDAC cases with genomic instability is enriched with *BRCA1*, *BRCA2* or *PALB2* mutations and a signature of DNA damage repair deficiency. These subtype of patients who displayed remarkable clinical response to DNA damaging agents thus suggesting the potential therapeutic effects of PARPi, extend beyond germline *BRCA 1/2* mutation carriers. *PALB2*, *Rad51*, *ATM*, *RPA1*, *FANCM*, *REV1L*, *XRCC* and *HUWE1* GAs lead to DNA repair defects and may represent potential targets for PARPi. Therefore, it is critical that we identify novel functional and cost-effective tools to identify high-risk DDR cases without the necessarily interrogating each of these genetic aberrations individually. Our group is studying this specific subgroup with clinical and translational studies.

Biography

Golan Talia is a Clinician-Scientist currently conducting translational laboratory research while also serving as the Medical Director in Chaim Sheba Medical Center. Her clinical interest is in patients with pancreatic cancer. She is developing an innovative model based on primary tumor cells obtained from patients' ascites. Her career goals include expertise in clinical medicine, translational laboratory research and drug development.

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