CARNA BIOSCIENCES

Carna Newsletter

Vol.19
2025.04.03

The involvement of extrachromosomal DNA (ecDNA) in intratumoral genetic heterogeneity and the potential of CHK1 inhibitors targeting ecDNA-containing tumors as next-generation cancer therapeutics

What is ecDNA?

Extrachromosomal DNA (ecDNA) is a major contributor to treatment resistance and poor outcome for patients with cancer, and it has recently attracted attention as a key player in new cancer molecular mechanisms. Individual ecDNA is circular and large, typically greater than 500 kilobases (kb) in size and often contains oncogenes. The non-chromosomal inheritance and resultant random segregation of ecDNA during cell division promotes intratumoral genetic heterogeneity[1)2)] (Fig.1). Highly accessible chromatin of ecDNA alters gene-regulatory architecture. Additionally, ecDNAs tend to cluster to form hubs and then the ecDNA hubs enable interactions between enhancers and promoters in trans. These characteristics demonstrate that ecDNA promotes massively elevated transcription of oncogenes, due to its elevated DNA copy numbers, highlighting a new mechanism by which ecDNA contributes to cancer pathogenesis[3)4)].

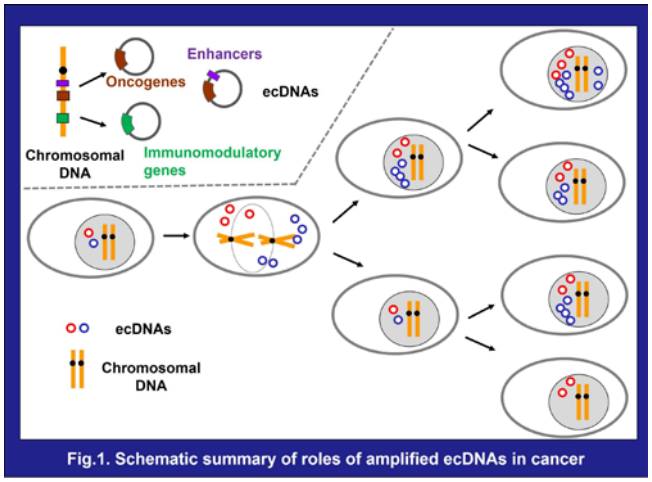

Fig.1. Schematic summary of roles of amplified ecDNAs in cancer

The involvement of ecDNA in cancer

It was demonstrated that 17.1% of tumor samples contained ecDNA by analyzing data from 14,778 patients with 39 tumor types from the 100,000 Genomes Project, led by the Francis Crick Institute, University College London in the UK, and Stanford University in the USA[1)]. In contrast, another study has reported that ecDNA amplification was nearly undetectable in normal tissue samples[5)].

Among tumors, ecDNA was frequently detected in liposarcomas, glioblastoma and HER2$^+$ breast cancer. Across all tumor types, oncogenes in the RTK-RAS (EGFR, ERBB2 and FGFR1), TP53 (MDM2) and cell cycle (CCND1 and CDK4) pathways were most commonly amplified on ecDNA. Moreover, ecDNA also frequently amplified immunomodulatory genes, and ecDNA carrying immunomodulatory genes were associated with reduced tumor T cell infiltration. Clinically, the potential of detecting ecDNA was higher in later stage tumors, and cancer patients with detectable ecDNA had shorter overall survival compared to those without detectable ecDNA. ecDNA amplification promotes intratumoral genetic heterogeneity, which may lead to poor outcomes, potentially through providing tumors with additional routes to circumvent treatments[1)5)]. Against this background, new approaches are currently being explored to develop drugs that can more effectively treat cancers driven by ecDNA.

The potential of Checkpoint kinase 1 (CHK1) as a therapeutic target

CHK1 has successfully been identified as an essential target for the survival of ecDNA-dependent cancer cells by CRISPR knockout screen using an ecDNA amplification model in HeLa cancer cells[6)]. In ecDNA-containing tumor cells, excessive transcription-replication conflicts lead to increase level of replication stress. In the absence of a functioning checkpoint, cells with highly damaged DNA proceed through the cell cycle, leading to accumulation of DNA damage and then cell death. As a master effector of S-phase checkpoint, CHK1 activation maintains cell viability by restricting cell cycle progression, limiting DNA replication to prevent excessive DNA damage accumulation, and

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orchestrating DNA repair[7] (Fig.2). Therefore, this suggests CHK1 inhibition as an effective therapy for ecDNA-containing cancers, as it prevents DNA damage repair and induces unscheduled replication and accumulation of excessive DNA damage, leading to cell death[8].

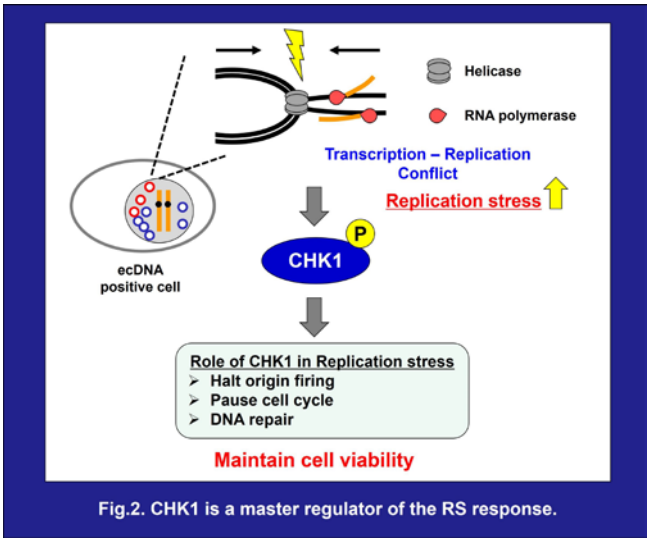

Fig.2. CHK1 is a master regulator of the RS response.

Anti-tumor effects of a CHK1 inhibitor, BBI-355

It was demonstrated that BBI-355, a selective small molecule inhibitor of CHK1, elevated markers of DNA replication stress in an ecDNA+ cancer cell line compared to its near isogenic ecDNA- one. Additionally, in multiple xenograft mouse models, implanted cancer cells with amplification of EGFR, CDK4, FGFR2 and MYCN respectively, BBI-355 demonstrated to inhibit tumor growth in all the models and enhance the anti-tumor effects in combination with the therapies targeting each ecDNA oncogene product[7]. BBI-355 is currently being studied in a first-in-human Phase 1/2 clinical trial in patients with oncogene amplified cancers. This may pave the way for the success of next-generation cancer therapies directing ecDNA.

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- Cell-based NanoBRET™ TE Intracellular Kinase Assay Services

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