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Mini Review

Extrachromosomal DNA as an Emerging Role in Cancer

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Introduction

Extrachromosomal DNA (ecDNA) refers to circular DNA segments, sometimes known as extrachromosomal circular DNA (eccDNA), which are located outside of the linear chromosome. The size of ecDNA varies from kilobases (kb) to megabases (Mb) [1-3]. ecDNA was not new since it was firstly discovered in 1965 as double minutes (DMs) from human neuroblastoma specimens [4]. It is commonly considered to originate from the deleted part of the linear chromosome via several known mechanisms, such as chromothripsis and genomic rearrangements caused by endogenous or exogenous stimulations, and it is reported to own the capability to re-integrate into linear chromosomes [5-8]. ecDNA consists of circularized DNA segments originating from either the same chromosome or the different chromosomes. ecDNA is not only found in human, but also in other eukaryotic species like yeast and Caenorhabditis elegans, suggesting a common phenomenon in eukaryotic cells [9,10]. Although ecDNA is relatively small-sized comparing with linear chromosome, recent studies have demonstrated the critical role of ecDNA to many diseases, such as cancer [11,12].

ecDNA is Highly Associated with Cancer

Cancer, to large extent, is characterized as the formation of aberrant genetic structures [8], where ecDNA generation is more frequent than that in normal tissues. This was confirmed by a recent study that ecDNA is commonly formed in various cancer types, in which glioblastoma, the cancer type with most frequent ecDNA formation, even shows an ecDNA-positive fraction over 50% [13]. Moreover, it showed that ecDNA content is significantly higher in patient-derived cultures than cancer cell lines. For instance, ecDNA is positively detected in nearly 90% of patient-derived glioblastoma cells and nearly 100% of patient-derived medulloblastoma cells [14]. Cancer develops frequently with the gradual acquisition of heterogeneity, which defines as the distinct morphological or functional profiles in a bulk tumor, resulting from the non-uniform distribution of genetic, transcriptomic and epigenetic alterations in the spatial and temporal manner [15]. Tumor heterogeneity contributes to drug resistance and poor prognosis [15]. ecDNA is considered to play the key role in tumor heterogeneity in respective of the discordant inheritance pattern and rapid amplification. A recent study has shown that ecDNA is the major cause of the genomic heterogeneity in glioblastoma, which is independent of alterations in linear chromosomes during tumor progression [16]. Another study has confirmed that ecDNA content is positively correlated with tumor heterogeneity in several cancer types, especially in patient-derived cultures of medulloblastoma and glioblastoma [14]. The existence of ecDNA in cancer cells contributes to several important properties and is recognized gradually as the major role in cancer development and progression. However, the detailed mechanism by which ecDNA functions inside the cancer cells is not fully revealed and still under investigation.

ecDNA Carries Oncogenes to Promote Carcinogenesis

As well as the principal aspect, several studies have reported that ecDNA carries oncogenes like MYC (ec-MYC), CDK6 (ec-CDK6), CCND1 (ec-CCND1) by using fluorescence in situ hybridization (FISH) or live-cell imaging achieved by clustered regularly interspaced short palindromic repeats (CRISPR) in cancer cells in metaphase [14, 17]. The results showed that ecDNA which is not overlapped with linear chromosome distributes discretely or aggregates to form ecDNA hubs in the nucleus [14, 18]. Moreover, excessive amplification of ecDNA results in aberrant copy number formation of oncogenes, which leads to ectopic expression of oncogenes and cancer development. Furthermore, ecDNA also carries mutant oncogenes like EGFRvIII that has a deletion of ligand-banding domain, leading to consistent activation and uncontrolled cell growth or survival comparing with wild type EGFR [19]. EGFRvIII is most abundantly found in glioblastoma, and amplification of ecDNA-EGFRvIII (ec-EGFRvIII) contributes to the dynamic drug resistance against tyrosine kinase inhibitors (TKI) targeting EGFR, such as lapatinib [20].

ecDNA Carries Enhancers to Promote Oncogene Expressions

Besides oncogenes, ecDNA can also carry regulatory elements such as enhancers, a type of DNA sequence containing short motifs and more accessible for sequence-specific transcription factors (TFs) binding to facilitate expression of target genes [21]. Enhancers are located at either upstream or downstream of target promoters. Enhancers are marked by multiple epigenetic signatures such as histone H3 lysine 4 monomethylation (H3K4me1) and H3K27 acetylation (H3K27ac) [22]. Recent study reported that ecDNA has lower order of chromosomal compaction, evaluated by assay for transposase-accessible chromatin using sequencing (ATAC-seq) and visualization (ATAC-see) [3]. In addition, chromatin immunoprecipitation followed by sequencing (ChIP-seq) of H3K4me1 and H3K27ac have revealed the presence of active enhancers on ecDNA [3].

Enhancers loading on ecDNA function as two regulatory patterns: intragenic (intra-ecDNA) or intergenic (inter-ecDNA or ecDNA to linear chromosome). Co-amplification of enhancer and oncogene both on ecDNA results in dramatic up-regulation of oncogene [23,24]. For example, EGFR and its enhancers are identified to co-localized in glioblastoma via ecDNA reconstruction based on whole-genome sequencing (WGS) and H3K27ac ChIP-seq [23]. This regulatory pattern allows distal interactions between enhancer and promoter which may jump over the insulator, an insulation element for blocking regulatory effect on enhancer to target promoter, and subsequently results in intensive expression of target oncogenes. Meanwhile, enhancer on ecDNA is capable to regulate oncogenes located in linear chromosome, which creates the intergenic interactions between ecDNA and linear chromosome.

Currently, super-enhancers (SEs), a cluster of proximate typical enhancers with high H3K27ac signals are identified on ecDNA in glioblastoma [25,26], which leads to genome-wide interactions between SEs on ecDNA and linear chromosomes via Hi-C and chromatin interaction analysis by paired-end tag sequencing (ChIA-PET) [27]. Multiple oncogenes are simultaneously activated by this kind of SEs, forming a hub together with transcription factors and co-activators. Additionally, SEs loading on ecDNA are mobile and serve as the free regulatory elements to promote oncogene expression in the global chromosomal scale [27, 28]. Furthermore, the contact frequency between SEs on ecDNA and target oncogenes on linear chromosome is positively related to its expression level [27]. These results demonstrate a novel pattern of oncogenes activation by global interactions between SEs on ecDNA with multiple oncogenes in linear chromosomes.

Conclusion

Cancer is a malignant disease with high heterogeneity and poor prognosis. However, there is still little information regarding the detailed mechanism on carcinogenesis. The role of ecDNA in cancer is overlooked during past few decades because of limited technologies. Nowadays, the significance of ecDNA has been paid more attentions. ecDNA has been considered as a cancer-related biomarker, and a screening of plasma ecDNA in cancer patients has made it as an effective tool in a minimum invasive manner [29,30]. Therefore, detecting ecDNA in cancer may be an effective way to achieve early diagnosis and accurate treatment.

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