Oncology and Translational Medicine
DOI 10.1007/s10330-015-0103-y

October 2015, Vol. 1, No. 5, P222–225

REVIEW ARTICLE

Novel patterns of cancer genome evolution

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Abstract

Cells usually undergo a long journey of evolution during the progression from normal to precancerous cells and finally to full-fledged cancer cells. Multiple genomic aberrations are acquired during this journey that could either act as drivers to confer significant growth advantages or act as passengers with little effect on the tumor growth. Recent advances in sequencing technology have made it feasible to decipher the evolutionary course of a cancer cell on a genome-wide level by evaluating the relative number of mutated alleles. Novel terms such as chromothripsis and chromoplexy have been introduced to describe the newly identified patterns of cancer genome evolution. These new insights have greatly expanded our understanding of the initiation and progression of cancers, which should aid in improving the efficiency of cancer management and treatment.

Received: 12 June 2015
Revised: 12 July 2015
Accepted: 25 September 2015

Key words: Cancer genome; evolution; chromothripsis; chromoplexy

Like all cells that constitute the human body, cancer cells contain a set of chromosomes consisting of genomic DNA and various associated proteins [1]. Nonetheless, the cancer genome often harbors numerous aberrations due to mutagens of both internal and external origin [2–3]. Exposure to mutagens such as tobacco smoke, ultraviolet light, or fungi-generated aflatoxins leads to increased rates of DNA lesions and, consequently, increased risks of cancer [2–3]. DNA aberrations include several different classes of sequence changes, such as single nucleotide variations (SNV), in which only one nucleotide is substituted; copy number variations (CNV) involving the gain or loss of whole chromosomes or focal regions of chromosomes, leading to the amplification or absence of the involved genes; and rearrangements that result from the breakage and re-ligation of double-stranded DNA within one or between multiple chromosomes [4–6]. A substantial amount of effort has gone into systematically characterizing the somatic events occurring in cancer genomes [4]. In one study, 208,311 primer pairs were designed from the complete protein-coding sequences of the human genome for polymerase chain reaction (PCR) amplification of DNA obtained from colon cancer, breast cancer, and glioblastoma. The PCR products were then subject to Sanger-based capillary sequencing to detect possible somatic events [7–8].

The advent of next-generation sequencing technology has greatly decreased the cost of deciphering the whole exomes or whole genomes of cancer samples [9]. Combined with advances in bioinformatics algorithms such as short read mapping, SNV and CNV calling, and rearrangement detection, great insights have been gained related to the mutational landscape of cancer genomes [4, 9–10]. Besides identifying the different mutation types, mutation rates, and affected genes and pathways, the evolutionary path of how cancer cells accumulate mutations has also been uncovered [5–6, 11–12]. Here, we focus on illustrating the novel evolutionary patterns of the cancer genome revealed by whole-genome sequencing of different types of cancers.

Chromothripsis

The term chromothripsis was coined during the screening for somatic rearrangements of the cancer genome in patients with chronic lymphocytic leukemia (CLL) [13]. One of the ten patients evaluated exhibited 42 rearrangements in the long arm of chromosome 4 with pronounced characteristics, including: (1) geographically confined localization of break points; (2) restricted copy number states that oscillate between one and two cop-

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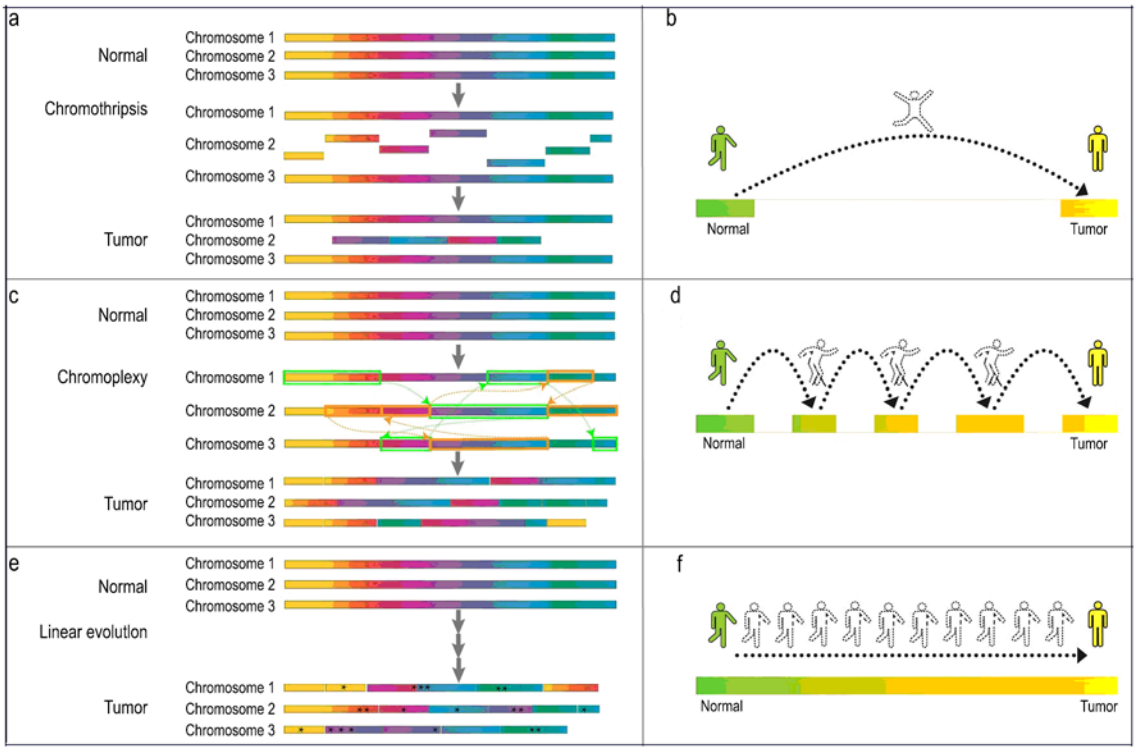

Fig. 1 Schematic representation of three patterns of cancer genome evolution. (a and b) Chromothripsis. One of the three chromosomes undergoes dramatic restructuring by shattering into pieces and then re-ligating them together, which could affect multiple cancer-related genes and allow for the affected cells to accomplish malignant transformation in a single event. However, most of the cells would likely not survive such a dramatic change and would be swept out; (c and d) Chromoplexy. Double-stranded DNA breaks occur in three chromosomes, which are realigned together within one or across multiple chromosomes, leading to milder rearrangement that could alter the expression pattern of one or a few genes. Multiple cycles of chromoplexies could occur during tumor growth, which would progressively increase the malignancy of tumors. Only one typical chromoplexy is shown in panel C; (e and f) Linear evolution. Point mutations ("*" in panel e) and chromosome rearrangements accumulate progressively during linear evolution, which usually spans a long period of time and leads to the successive presence of multiple tumor subclones

ies; (3) complex rearrangements spanning the involved region that comprised 8 deletions, 9 tandem duplications, 6 head-to-head inversions, and 10 tail-to-tail inversions [13]. This pattern is strikingly different from the patterns of genomic instability that are typically seen in breast, lung, or pancreatic cancer, where rearrangements tend to be either scattered genome-wide or, if localized, are associated with substantial genomic amplification [14–16]. By analyzing the copy number profiles of 746 cancer cell lines and 2792 cancer specimens obtained using high-resolution single nucleotide polymorphism arrays [17–18], it was found that 2%–3% of cancers of different types, such as melanoma, small cell lung cancer, glioma, hematological malignancies, non-small cell lung cancer, and synovial sarcoma, exhibited the rearrangement pattern of chromothripsis [13]. Massively parallel paired-end sequencing and cytogenetic studies were carried out in SNU-C1, 8505C, TK10, and SCLC-21H cells, and the existence of complex genomic rearrangements was confirmed in all four cell lines.

It is hard to explain how such complex restructuring of a chromosome could appear using the conventional model, which generally assumes that rearrangements occur sequentially and independently of one another over many cell cycles, leading to an increasingly disordered genomic structure [1, 12, 19]. Therefore, a new model was proposed stating that the majority of overwhelming rearrangements might occur in a single catastrophic event, during which the chromosome or chromosomal region shatters into tens to hundreds of pieces, some (but not all) of which are then stitched together by the DNA repair machinery in a mosaic patchwork of genomic fragments (Fig. 1a and 1b) [13]. This catastrophic model provides reasonable explanations for all of the characteristics of chromothripsis. Further studies indicated that chromothripsis could confer a significant selective advantage to a cell and make it take a considerable leap along the road to cancer [13]. In the small lung cancer cell line SCLC-21H, chromothripsis leads to markedly increased copy numbers of the *MYC* oncogene. In one chordoma sample, chromothripsis was found to lead to the deletion of the *CDKN2A* gene, and was also shown to result in the loss of both *CDKN2A* and miR-15a/16-1, the microRNA cluster deleted in > 50% of CLL patients. Micronuclei, which are small, extranuclear

bodies generated from lagging chromosomes during erroneous mitotic chromosome segregation, provide one explanation of how chromosomes are pulverized into small pieces during chromothripsis [20–21]. Whole chromosome-containing micronuclei can persist in cells over several generations. Chromosomes in micronuclei undergo defective and asynchronous DNA replication, resulting in extensive DNA damage and chromosome fragmentation that could be integrated back into the genome or stitched together to form a heavily restructured chromosome [20]. Many genotoxic reagents such as radiation and harmful chemicals can trigger the formation of micronuclei [21].

Chromoplexy

While performing whole-genome sequencing and DNA copy number profiling of 57 prostate cancer samples, Baca *et al* defined a spectrum of oncogenic events that occur during prostate tumor development [6]. Detailed examination of these chromosomal rearrangements revealed a distinctive pattern of a "closed and balanced chain", which denotes that during the exchange of inter- and intra-chromosomal segments, no concomitant losses occur in any chromosome arms, although losses of some genetic materials (sometimes rather long) are possible [6, 22]. One noteworthy closed chain of rearrangements was found to harbor breakpoints situated in close proximity to multiple known cancer genes or orthologs, such as TANK-binding kinase 1 (*TBK1*), *TP53*, *MAP2K4*, and *ABL1* proto-oncogene [22]. This phenomenon was described as chromoplexy, derived from the Greek term "-plexy" meaning to weave or braid. A probabilistic model was created to investigate whether the rearrangements in chromoplexy might arise independently of one another. Comparison with simulated genomes and "scrambled" genomes indicated marked deviation from reference genome locations, in which both breakpoints in one arrangement were closer to breakpoints of other arrangements than expected by chance, suggesting that the rearrangements in chromoplexy may occur in a coordinated manner [6]. An algorithm called ChainFinder was created, which employs a statistically based search rooted in graph theory, to identify genomic rearrangements that deviate significantly from the independent model, and thus appear to have arisen in an interdependent fashion. A systematic survey using ChainFinder indicated that 50 out of 57 tumors contained chromoplexy-related chains with five or more rearrangements (corresponding to ten or more breakpoints considering that each rearrangement has two breakpoints) (Fig. 1c and 1d) [6]. In some cases, a chain could contain more than 40 rearrangements involving the weaving of five or more chromosomes. Fusion of the oncogenic *ETS* gene occurs in roughly half of prostatic adenocarcinomas [23–24]. It was found that *ETS+* tumors produced significantly more interchromosomal rearrangements than *ETS–* tumors and involved a greater maximum number of chromosomes in a single event [6]. Several cancer genes have been identified as recurrently deleted or rearranged by chromoplexy, including *PTEN*, *NKX3-1*, *CDKN1B*, *TP53*, and *RB1* [6].

Linear evolution

In contrast to chromothripsis and chromoplexy, during which somatic aberrations arise in a catastrophic event or in a relatively short time frame, linear evolution describes the phenomenon in which somatic mutations are gradually accumulated over a long period of time (Fig. 1e and 1f) [1, 19]. In fact, linear evolution represents the classical view of how a cell evolves from its normal status to the malignancy status through a series of genome alterations, and is supported by observations in invasive colorectal cancer, which usually emerges from an antecedent benign adenomatous polyp, and cervical cancer, which proceeds through intraepithelial neoplasia [1, 19, 25]. Whole-genome studies of acute myeloid leukemia (AML) patients by next-generation sequencing demonstrated the progressive acquisition of SNVs in the cancer genome during the relapse of chemical drug-resistant clones [11–12]. The number of clones and the mutations each clone carried were identified from a density plot of the variant allele frequency in both primary and relapsed tumor samples [12]. Some tumor clones, usually including the founding one that comprises most of the tumor cells, were swept out by a combination treatment of multiple drugs. However, one new clone would usually emerge during the treatment and become therapy-resistant by obtaining a few novel mutations, which would eventually lead to patient expiration [12]. Thus, the evolution of AML genomes displays a linear pattern that more closely resembles the conventional view of cancer genome evolution.

Conclusions

The three evolutionary patterns summarized in this review represent a continuum of cancer genome alteration mechanisms that may operate separately or coordinately in the progression of a particular tumor. Chromothripsis can dramatically reshape a focal region of a chromosome or a whole chromosome in a single catastrophic event. A precancerous cell could obtain numerous advantages via chromothripsis, although most of the cells will probably not survive the detrimental effects of extensive genome rearrangements. On the opposite end of the spectrum, the linear evolution model argues that both passenger-like and driver-like alterations accumulate in a cancer genome gradually over numerous cell divisions through point mutations, simple translocations, and focal copy num-

ber alterations. Between the two extremes, chromoplexy restructures cancer genomes in a punctuated fashion, analogous to the observation of the punctuated evolution of species between periods of mutational equilibrium. A given cancer type can adopt any one, two, or even all three of these evolutionary mechanisms to disrupt various cancer-restraining processes. Whole-genome sequencing data show potential to effectively capture aspects of the "molecular archeology" of cancer development.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-015-0103-y
Cite this article as: Zhang X, Deng XD, Zhang Y, *et al*. Novel patterns of cancer genome evolution. Oncol Transl Med, 2015, 1: 222–225.