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Chromothripsis in congenital disorders and cancer: similarities and differences

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Genomic rearrangements may give rise to congenital disease and contribute to cancer development. Recent evidence has shown that very complex genomic rearrangements in cancer cells can result from a single catastrophic event of massive DNA breakage and repair, termed chromothripsis. This results in heavily rearranged chromosomes comprising frequent sequence losses. A very similar process of chromosome shattering is found for complex chromosome rearrangements in the germline of patients with congenital disorders. Here, we review the literature on chromothripsis in cancer and congenital disease. We describe differences and similarities for chromothripsis rearrangements in somatic tissue and the germ line and we discuss the cellular origin and molecular mechanisms of chromothripsis.

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Chromosome shattering in human genomes

Structural genomic variation such as deletions, inversions or duplications impact a major part of the human genome [1]. If structural changes occur *de novo* either in somatic cells or in the germline, this may cause disease. Occasionally, structural genomic rearrangements can be very complex, involving multiple breakpoints [2,3]. In their landmark paper in Cell, Stephens *et al.* used a combination of SNP array profiling and paired-end next generation sequencing to reveal very complex somatic rearrangements in cancer genomes [4••]. On the basis of the characteristics of these rearrangements they suggested that chromosomes are locally shattered to pieces in a single catastrophic event followed by reassembly of these pieces into mosaic chromosomes (Figure 1a). A new term, chromothripsis, was introduced to indicate these catastrophic DNA rearrangements. Chromothripsis is Greek for chromosome (chromo) and shattering to pieces (thripsis). At about the same time, we found that complex rearrangements in patients with congenital disease, such as mental retardation, resulted from a very similar chromosome shattering process as observed in tumor genomes and therefore the term chromothripsis is appropriate here too [5••].

Characteristics of chromothripsis in cancer and developmental disease

Chromothripsis is characterized by several distinct features that distinguish it from other complex rearrangements. Furthermore, these features provide insight into the mechanism of origin. We will highlight the main genomic hallmarks of chromothripsis and describe differences and similarities between somatic events in cancer and germline events in congenital disease below.

Localization and characteristics of DNA breaks

Chromothripsis in cancer genomes involves tens to hundreds of genomic rearrangements on one or multiple chromosomes [4••]. The number of breaks is substantially lower for chromothripsis rearrangements seen in the germline, where chromothripsis with up to 24 breaks has been described [6•]. A first striking observation that marks the chromothripsis rearrangements seen in cancer and congenital disease is the strong clustering of breakpoints in the genome [4••,6•]. The rearrangements are typically affecting confined regions on only one or a few chromosomes. Although, for congenital chromothripsis rearrangements there are mostly multiple chromosomes reported (9/11 published cases), in cancer there are many reported examples of chromothripsis affecting just a single chromosome [4••,7–9,10••]. Besides localization to one or a few chromosomes, breakpoints tend to cluster together in small regions within rearranged chromosome arms. Part of this clustering of breaks in small regions is explained by repair of both break-ends resulting from a clean double-strand DNA break [4••] (Figure 1b). Particularly for congenital chromothripsis rearrangements such signatures of double-strand DNA breaks are found and the exact break-end positions are often one or just a few nucleotides apart [5••,6•,11•], while cancer chromothripsis displays less precisely paired break-ends. Possibly, in cancer chromothripsis the break ends could be more heavily resected by nuclease activity following formation of staggered or damaged DNA overhangs after breakage, compared to congenital chromothripsis [12].

Hundreds of breakpoint junctions have been analyzed for chromothripsis rearrangements in cancer and congenital

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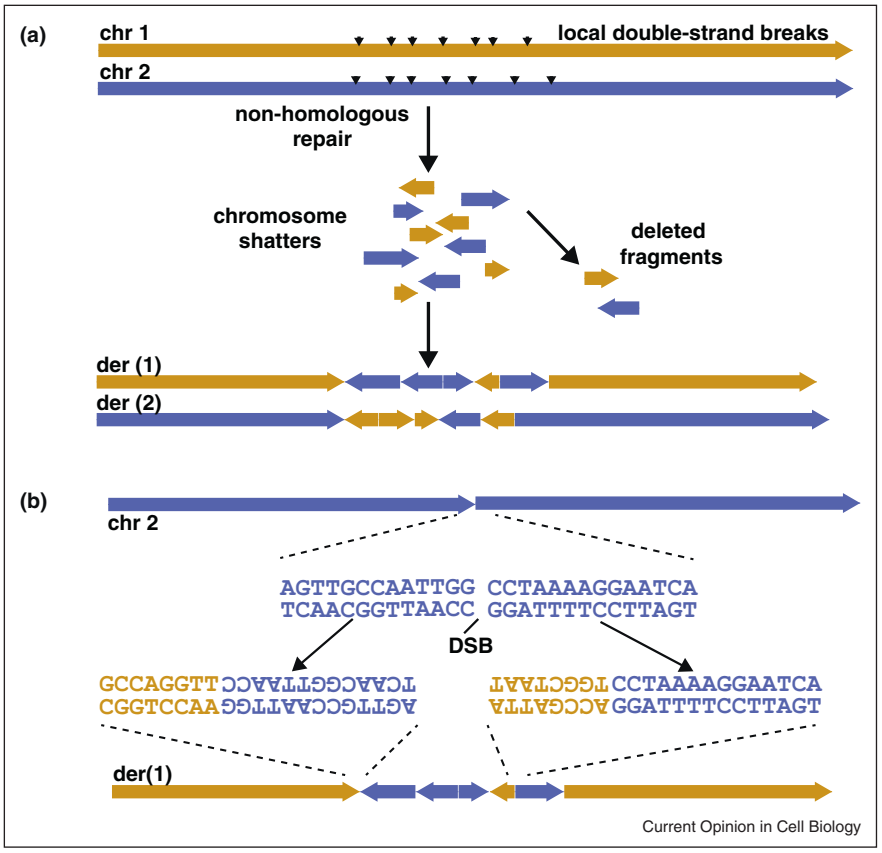
Figure 1



(**a**) Schematic overview of the chromothripsis process. (**b**) Example of repair of two break-ends resulting from a single double-strand break (DSB) on chr 2. The break-ends are fused to other fragments resulting from DSBs on chr 1. Such reciprocal repair of both break-ends is typically seen for chromothripsis rearrangements.

disease to identify signatures of repair mechanisms. A large fraction (>50%) of the fused DNA segments at breakpoint junctions do not show any homology and involve blunt fusions or small insertions, while the remainder display microhomology of just one or a few nucleotides. This demonstrates that chromothripsis break repair involves nonhomologous processes [4••,6•,10••,11•].

Chromothripsis and copy number changes

The chromothripsis rearrangements found in cancer involve frequent oscillation of regions with a high copy number state and regions with a low copy number state, which show loss of heterozygosity [4••]. This is a direct consequence of chromosome shattering by many simultaneous DNA breaks and stitching back together of the resulting DNA fragments, during which some fragments are retained and others are lost (Figure 1a). Related to this, selection processes during cancer development lead to amplification of genomic fragments including oncogenes by formation of double-minute chromosomes following chromothripsis [4••,10••]. In contrast to the many changes between two copy states in cancer chromothripsis, a striking characteristic of congenital chromothripsis rearrangements is their relatively balanced state, despite the presence of multiple DNA breaks across several chromosomes [5••,6•,11•]. For example, we have observed completely copy neutral chromothripsis rearrangements in a patient, while 24 breaks had occurred on five chromosomes [6•] (Figure 2). Occasional deletions were also found in some patients, but copy gains have not been observed [5••,6•,11•].

These lower numbers of breaks and copy number changes in congenital chromothripsis may reflect differences in the molecular mechanisms that give rise to chromothripsis in developmental disease and cancer. Furthermore, selection is another factor that may strongly influence our observations of chromothripsis, because we only observe the viable end-stage. More breakpoints and more copy number changes obviously increase the risk for a nonviable outcome in both cancer and embryonic

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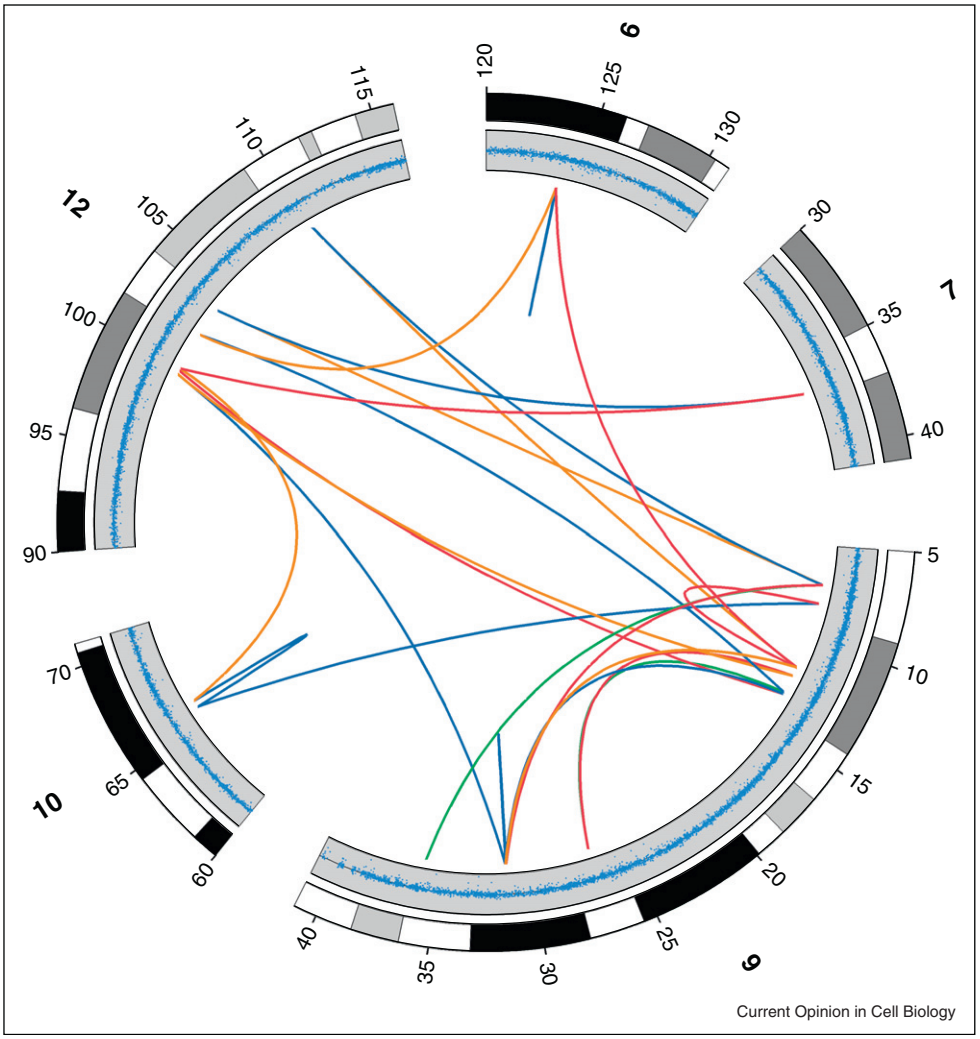
Figure 2



Typical example of chromothripsis rearrangement in congenital disease. The circos plot displays copy neutral chromothripsis rearrangements in a patient with a congenital disorder (adapted from [6•]). The outer circle displays the chromosome ideogram and the inner circle displays the copy number profile based on SNP array data. The lines indicate breakpoint junctions. Blue, tail-to-head; green, head-to-tail; red, head-to-head; yellow, tail-to-tail.

development, but the effect is likely much stronger in a developing embryo. Finally, it should be noted that the observed differences may result from different experimental setups. Copy-neutral chromothripsis events cannot be identified by copy number profiling and are therefore systematically missed when this technique is applied as a first line screening.

Single event versus multistep model

A major debate centers around the fact whether chromothripsis emerges as a single catastrophic event or rather results from multiple consecutive DNA breakages and repair [13]. In fact, there is no direct experimental data that show that chromothripsis shattering occurs in a single massive event, neither for cancer nor for congenital disease. The original paper by Stephens *et al.* describes simulations to model the outcome of progressive accumulation of breaks versus simultaneously acquired breaks [4••]. These simulations indicate that the many alternations between two copy number states and the loss of heterozygosity of the lower copy state can only reasonably be explained by many simultaneous breaks.

The enormous complexity of chromothripsis breakpoints in tumor genomes and the heterogeneity of tumor samples make it difficult to reconstruct rearranged chromosomes and derive models for their formation. In

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patients with congenital disorders this is much more straightforward because the numbers of breaks are lower (typically 10–20) and there is no heterogeneity within a sample [6•]. It can be observed that congenital chromothripsis rearrangements have a similar architecture as for a simple reciprocal translocation, which involves only two breaks followed by formation of two derivative chromosomes (Figure 3a). It goes without saying that a reciprocal translocation is formed in a single event and not by two separate breaks in two cell cycles. Similarly, one can explain the formation of a reciprocal three-way translocation as a result of three simultaneous breaks on three chromosomes (Figure 3b). In addition, an inversion at a reciprocal translocation breakpoint can only occur simultaneously with the translocation breaks, unless one of the inversion breaks occurs at the exact same position as the translocation break albeit at a later time point, which is highly unlikely (Figure 3c). What we observe in the case of chromothripsis rearrangements in patients with developmental disorders is exactly the same: the outcome involves reciprocal rearrangements, albeit much more complex than a simple reciprocal translocation (Figure 3d). Seen from this perspective, constitutional chromothripsis rearrangements should have occurred in a single event involving many double-strand DNA breaks [6•]. It should be mentioned, though, that *de novo* rearrangements resulting from chromothripsis may trigger chromosomal instability in subsequent cell divisions via other mechanisms, for example, due to the absence of proper templates for homologous repair.

Incidence of chromothripsis

The signature of chromothripsis was found in 2–3% of all cancers [4••], but seems particularly prevalent in bone cancers (25%). Follow-up studies confirmed the presence of chromothripsis in several cancer types, including colorectal cancer, acute myeloid leukemia, multiple myeloma, neuroblastoma and medulloblastoma [7–9,10••,14]. A large survey of copy number profiles of 764 cases of multiple myeloma identified chromothripsis in 1.3% of the samples [9]. Furthermore, analysis of a large cohort of medulloblastoma revealed chromothripsis in 13 out of 98 cases (13%) and screening of 108 acute myeloid leukemia patients revealed chromothripsis in nine cases (8%) [10••].

The chromothripsis cases found in medulloblastoma and acute myeloid leukemia cohorts were strongly associated with mutations in TP53 [10••]. There are several explanations for the observed association between chromothripsis and TP53 mutations. Aberrant p53 functioning affects cell cycle control and limits apoptosis, promoting survival of cells with massive DNA damage. Furthermore, reduced p53 levels favor nonhomologous mechanisms of DNA repair, which is a hallmark of chromothripsis. It is not clear whether TP53 mutations are essential for chromothripsis to occur in all tumor types. Certainly, the observed link with TP53 mutations does not hold true for congenital chromothripsis. In most congenital cases the chromothripsis occurred *de novo* and all parents were healthy without any reported TP53 mutations [5••,6•,11•].

In patients with congenital disease the incidence of chromothripsis is less clear, primarily because no systematic screens for chromothripsis have been performed in large cohorts of patients. We analyzed the genomes of 10 patients with known complex genomic rearrangements (>2 visible cytogenetically visible breakpoints) and found chromothripsis in eight cases [6•], indicating the frequent occurrence of chromothripsis underlying congenital complex genomic rearrangements. In another study of 52 patients with karyotypically balanced rearrangements two *de novo* chromothripsis rearrangements were reported [11•].

Many complex genomic rearrangements involving multiple chromosomes have been described for patients with congenital disease. In all cases where complex rearrangements appear copy neutral or involve multiple chromosomes, chromothripsis may be a likely underlying phenomenon. In fact, several studies examining complex genomic rearrangements showed that all cases only involve deletions or are copy neutral, while duplications were not found [15–18]. These observations support the notion that chromothripsis may frequently underlie complex genomic rearrangements in patients with congenital disorders [6•].

Complex genomic rearrangements involving template switching

Analysis of complex chromosomal copy number changes in patients with developmental disorders showed that a mere process of chromosome shattering and stitching back together of chromosomal pieces may not be applicable for all complex germline rearrangements. Several complex rearrangements involving multiple deletions, duplications and triplications along a single chromosome have been described [19••]. These complex copy number changes can be explained by multiple template switching events following stalled replication forks [20]. Liu and coworkers introduced the term chromoanasynthesis (repeated chromosome synthesis) to indicate these complex rearrangements. Although the complex genomic rearrangements may resemble chromothripsis events in cancer because of the many copy number changes along a chromosome, a major difference is that the rearrangements are not limited to two copy states as is the case for chromothripsis rearrangements [4••,6•]. Furthermore, these complex copy number changes appear restricted to a single chromosome and do not involve frequent translocations of genomic segments [19••]. Detailed analysis of breakpoints of patients

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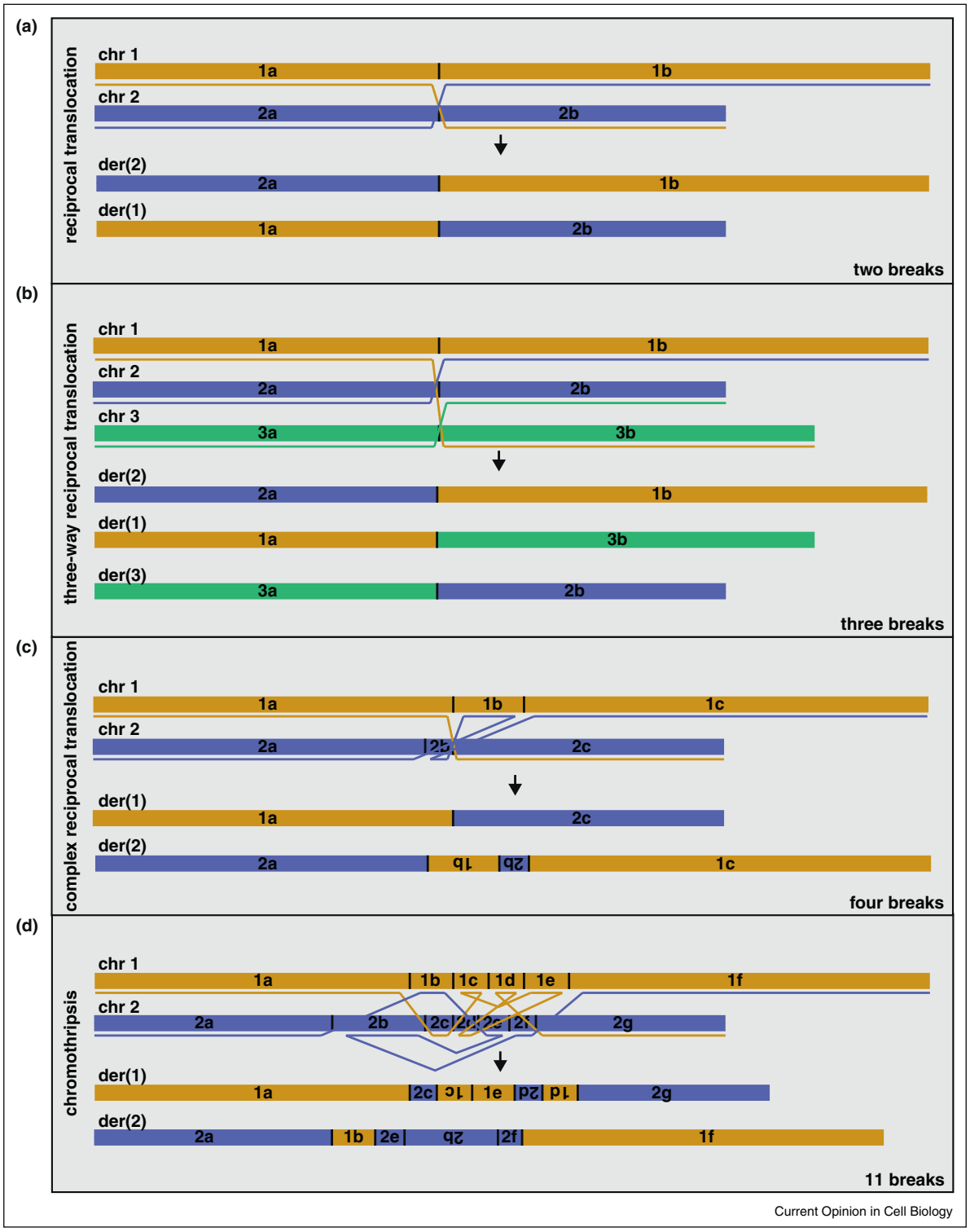
Figure 3



Overview of the relation between simple reciprocal translocations and chromothripsis: (**a**) reciprocal translocation, (**b**) three-way translocation, (**c**) complex reciprocal translocation, and (**d**) chromothripsis. The figure illustrates that chromothripsis may just be a more complex variant of a simple reciprocal translocation.

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with complex copy number changes has shown that the characteristic double-strand break signatures that are found in chromothripsis have not been observed in these rearrangements, supporting two classes of complex genomic rearrangements [6•]. A recent publication suggested using the term chromoanagenesis ('chromo' for chromosomes and 'anagenesis,' for rebirth) to capture both rearrangements types resulting from chromosome shattering and multiple template switch events, respectively [21].

Possible molecular causes of chromothripsis

The most striking experimental evidence for a possible mechanism leading to chromothripsis came from a study by Crasta *et al.*, which demonstrated that chromosome pulverization may occur as a result of chromosome missegregation in mitosis [22••]. According to this mechanism, chromosome segregation errors lead to lagging chromosomes, which end up in micronuclei. Defective and asynchronous replication of the chromosome within a micronucleus generates DNA damage and extensive DNA pulverization [22••]. Pulverized chromosomes may result from premature chromosome compaction of partially replicated chromosomes [22••,23]. Chromosomes in micronuclei can reincorporate in the nuclei of daughter cells and become stably maintained over subsequent cell divisions, but it is not clear if the chromosome pulverization in micronuclei eventually leads to daughter cells with the same complex rearranged chromosomes as seen for chromothripsis in cancer samples, including alterations between only two copy number states [4••].

Further hypotheses on the triggers of chromothripsis rearrangements involve exogenous sources of DNA damage such as ionizing radiation or free radicals that induce DNA breaks when the DNA is in a condensed state during mitosis [24]. In addition, induction of DNA replication stress by inhibition of DNA polymerase activity may induce complex genomic rearrangements through replication fork collapse and subsequent template-switching events [25]. In this context, genomic instability may result from stalling and collapsing of replication forks induced by activation of oncogenes [26], providing an endogenous molecular trigger for formation of complex genomic rearrangements in cancer cells. However, it should be noted that it is unclear if these triggers of DNA damage lead to chromosome shattering by double-strand breaks as observed for chromothripsis in cancer and development [4••,5••]. The rearrangements resulting from collapsed replication forks rather fit with a model of chromoanasynthesis. Finally, many examples of chromothripsis rearrangements in cancer involve regions extending to telomeres [4••]. This suggests that the breakage fusion bridge cycle involving dicentric chromosomes resulting from end-to-end chromosome fusions may cause catastrophic DNA breakage when centromeres are pulled to opposing poles. However, many consecutive breakage-fusion-bridge cycles will readily lead to genomic amplification, which is not seen for chromothripsis [24].

The origin of chromothripsis rearrangements in congenital disorders

Although the triggers for congenital chromothripsis rearrangements are not clear, there are some indications, which hint at an origin in the paternal germline [5••,6•]. The evidence for this stems from genotyping of common SNP positions in heterozygous deletions resulting from chromothripsis. Previous reports of complex genomic rearrangements and reciprocal translocations also suggested a strong paternal bias [16,17,27].

Constitutional chromothripsis rearrangements characterized so far, involve reciprocal rearrangements often on multiple chromosomes (e.g. five, see Figure 2). There have not been any reported cases of *de novo* chromothripsis rearrangements involving multiple chromosomes for which only one or a few of the derivative chromosomes are found in a patient. Therefore, it seems less likely that chromothripsis occurs during premeiotic cell divisions in spermatogenesis or during meiosis I. If so, this would quickly result in separation of derivative chromosomes and subsequent unbalances extending toward telomeres in sperm cells (Figure 4). On the basis of these arguments, chromothripsis could possibly occur after paternal meiosis during spermiogenesis [28]. Extensive chromatin remodeling takes place during DNA condensation during spermiogenesis and the incorrect processing of programmed breaks induced in this process may lead to DNA fragmentation [29]. Because spermatids lack sister chromatids for homologous recombination, double-strand break repair relies on error-prone nonhomologous end-joining. In addition, exogenous induction of DNA breaks in late spermatogenesis by ionizing radiation may result in genomic aberrations in the subsequent zygote and repair of breaks in sperm DNA is dependent on repair mechanisms in the zygote [30].

Although current data for congenital chromothripsis favor an origin in the paternal germline, we cannot exclude the occurrence of chromothripsis in early embryonic development. In fact, there is evidence for frequent genomic instability in human cleavage stage embryos derived from *in vitro* fertilization [31]. The chromosomal missegregation observed in cleavage stage embryos could possibly also give rise to complex genomic rearrangements following chromosome pulverization in micronuclei [22••] and consequently lead to individuals with mosaic chromothripsis, similar as for somatic events as observed in cancer.

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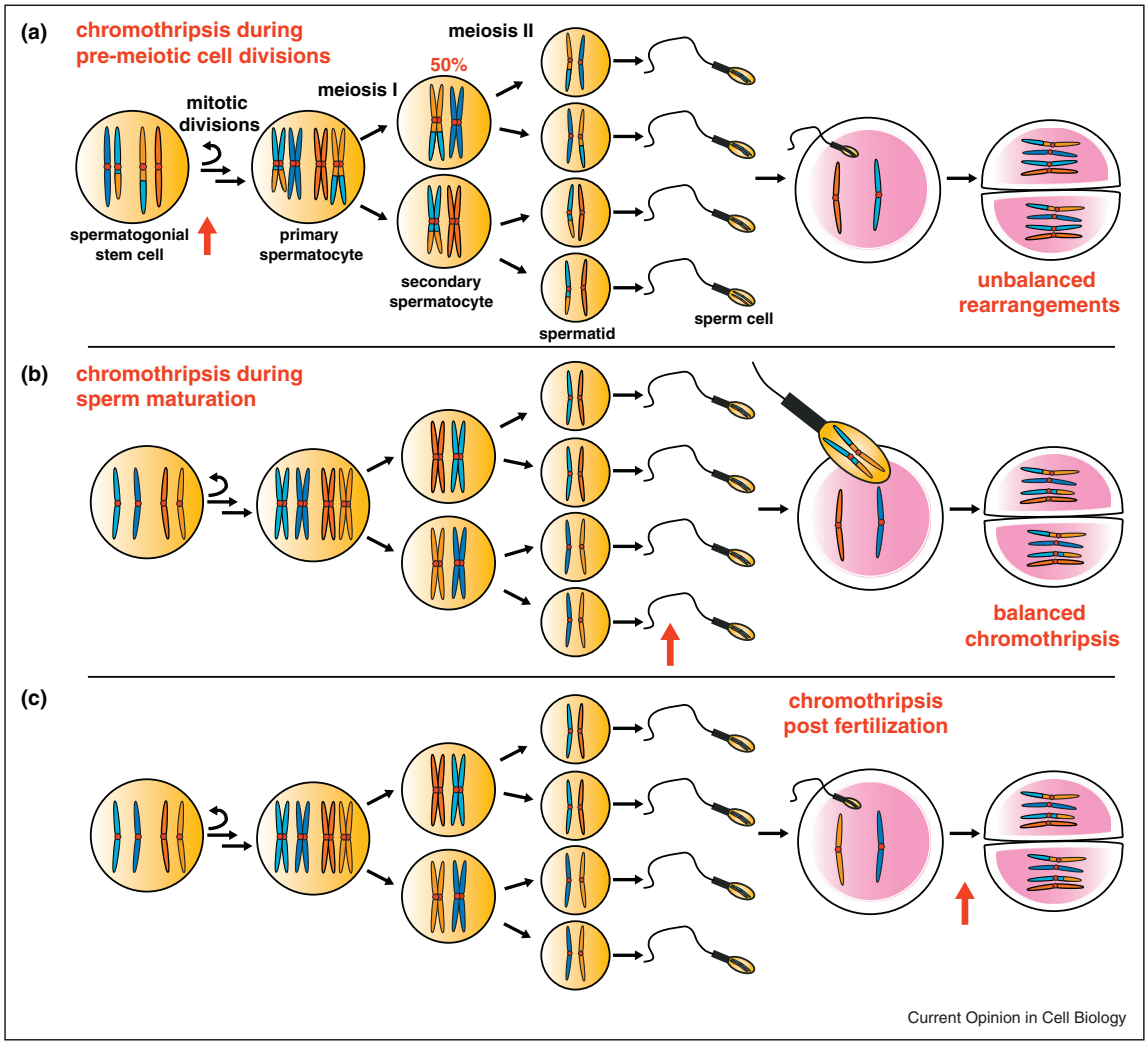
Figure 4



Overview of spermatogenesis and possible timepoints at which chromothripsis may occur in the male germline and post fertilization (red arrow). (**a**) If chromothripsis occurs during premeiotic divisions or during meiosis I, this can easily lead to imbalances in the resulting sperm cells and zygote, especially if the number of involved chromosomes increases. (**b**) The relatively balanced state of constitutional chromothripsis rearrangements can be nicely explained when assuming that chromothripsis occurs during maturation of sperm cells during spermiogenesis. (**c**) Alternatively chromothripsis may occur post fertilization during cleavage divisions.

Concluding remarks

The human genome continuously changes its shape by acquiring genetic changes in both somatic and germ cells. Chromothripsis represents a process of extreme reshuffling of the human genome. Although the devastating consequences of chromothripsis could readily lead to cell death, the rearrangements may also contribute to tumorigenesis and developmental disease by formation of fusion genes, altered gene expression, gene disruption or gene amplification. Several of such effects have already been reported and the near future will certainly bring numerous examples of disease with a driving role for chromothripsis.

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