Review Article

Chromosome Structural Alteration an Unusual Abnormality Characterizing Human Neoplasia

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Abstract

Background and Aim: Ring chromosomes are rare cytogenetic abnormalities that occur in less than 10% of hematopoietic malignancies. They are rare in blood disorder. The present review has focused on the ring chromosome associated with oncology malignancies.

Materials and Methods: By reviewing the web-based search for all English scientific peer review articles published, was initiated using Medline/PubMed, Mitelman database (http://cgap.nci.nih.gov/Chromosomes/Mitelman), and other pertinent references on websites about ring chromosomes in Oncology. The software program as End Note was used to handle the proper references for instruction to author. Karyotype descriptions were cited according to ISCN.

Conclusion: Ring chromosomes are rare chromosomal aberrations, almost many times are of *de novo* origin, presenting a different phenotype regarding the loss of genetic material. The karyotype represents the main analysis for detection of ring chromosomes, but other molecular technics are necessary for complete characterization. The information of this review article adds to the spectrum of both morphology and genetic rearrangements in the field of oncology malignancies.

Keywords: Ring chromosomes, Marker, Malignancy, Mechanisms, Abnormality

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Introduction

After the first report of a ring chromosome in a case of human leukemia by Sandberg et al.,1962[1], ring chromosomes have been infrequently (less than 10%) detected in hematopoietic neoplasias[2]. Whereas constitutional ring chromosome are rare, occurring in approximately 1 in 25000 human fetuses[3]. A ring chromosome, which appears to be a rare event in prenatal or cancer patients, can be formulated by fusions between both arms of the same chromosome with or without loss of genetic material.

Ring chromosome structure is relatively conserved[4] considering that ring chromosomes are rare in acute

myelogenous leukemia (AML)[5]. Most of the ring chromosomes were embedded in highly complex karyotypes. This suggests that the ring chromosomes were secondary changes in the course of disease progression[6]. There was no detailed, confirmatory report on an association between a certain leukemia subtype and a specific ring chromosome[5]. There is a review summarizes a great number of reports on a total of 760 ring chromosomes in human neoplasias at different sites, but includes only cases with clearly identified rings[2,7].

On rare occasions, ring chromosomes can found as constitutional aberrations in foetuses or new-born with developmental abnormalities. More commonly, they may arise as acquired genetic abnormalities in cells from tumors or leukaemias[8].

Carriers of a ring chromosome 22 are mentally retarded and show variable facial dysmorphism. They may also present with features of neurofibromatosis type II (NF2) such as vestibular schwannomas and multiple meningiomas[9].

Materials and Methods

Inclusion criteria for this review were original documents, systemic review possessing qualitative and quantitative research, and published in English from January 1962 through December 2015 to assess existing knowledge on relationship between ring chromosome and patients with blood disorder. In the search process for the literature the authors retrieved documents that contained malignancy, structural and numerical abnormalities, ring chromosome, heterogeneous population, cancer sites for cancer registration; the most scientific databases were searched. English abstract, and full text of ProQues, MEDLINE/PubMed, CINAHL, (MeSH terms), Mitelman database were included. The main keywords included, human, ring chromosomes, Marker chromosome, oncology, malignancy, mechanisms, structural abnormality, review article. Articles that were not directly relevant to our specific objective questions were excluded. The software program as End Note was used to handle the proper references for instruction to author. Karyotypic descriptions were cited according to ISCN (1995)[19].

Mechanisms of Ring Formation

Ring chromosomes at cell division: In contrast to linear chromosomes, rings may undergo cell division in three different ways[10,11]. Which of these pathways a ring chromosome will follow depends on the number of sister chromatid exchanges (SCE) that has occurred in the ring before cell division:

1. No SCE or an even number of SCEs in the same direction will enable normal, symmetrical segregation of the chromatids.
2. An even number of SCEs in different directions will lead to the formation of interlocked rings.

An odd number of SCEs will lead to transformation from two parallel chromatids into one continuous ring, similar to a Mobius band with the double size of the original rings (Figure 1).

Ring chromosomes may be formed in two ways in Figure 2.

1. By two DNA breaks, one in each arm of the same chromosome, followed by fusion of the proximal broken ends. The causes of these DNA breaks are usually unknown and so is the mechanism behind ligation of the ends. It is possible that the non-homologous end-joining machinery plays a role in this process[12]. A ring can also be formed by fusion at two breakpoints in the same chromosome arm. However, only few examples of such rings have been described. Most probably, this is because they are acentric and will lack attachment point for the cell division machinery. Unless there is a different anchorage sequence for the kinetochore complex they will be lost in subsequent mitoses. Such "neocentromere" sequences have, however, been described in rare cases of constitutional[13] and acquired[14] ring chromosomes.
2. By fusion of dysfunctional telomeres from the same chromosome. Several *in vitro* and animal models have shown that shortening of telomeric DNA repeats leads to the detachment of protective proteins from the chromosome ends[15]. This renders the chromosome ends prone to recombination with DNA either from other chromosomes leading to formation of a dicentric or with the other arm of the same chromosome leading to formation of a ring.

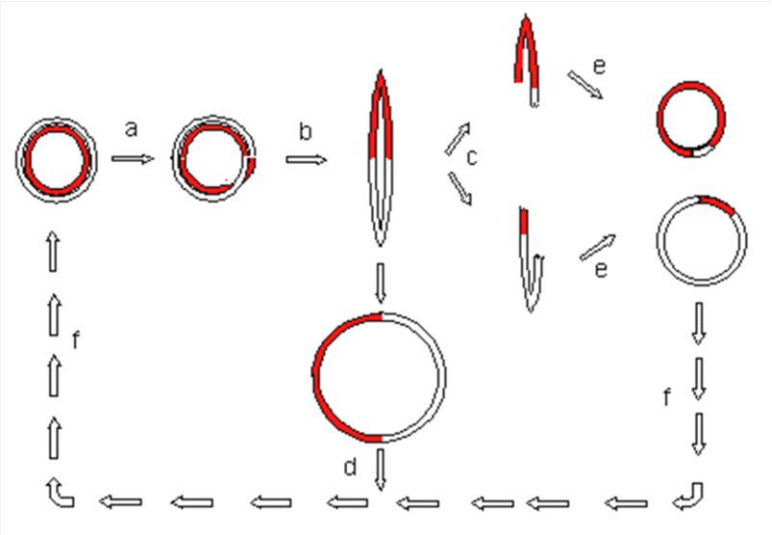

Figure 1. Breakage-fusion-bridge cycle triggered by a sister chromatid exchange (a) leading to bridge formation (b) and breakage (c), or nondisjunction (d) at anaphase. Broken ends fuse in the daughter cells (e) and form novel ring structures, which can again undergo the

Constitutional Ring Chromosome

Constitutional ring chromosomes occurs in 1/50000 human fetuses[3]. In most instances, these rings are formed by breakpoints in both arms, followed by fusion of the proximal ends into a ring with loss of the distal material. Such rings may thus result in clinical features mimicking terminal deletion syndromes. Alternatively, congenital ring chromosomes are supernumerary, i.e. they occur together with two normal homologues of the corresponding chromosome[16], and the consequences will be similar to partial trisomies or duplications. The ring syndromes are thus a very heterogeneous group, with different characteristics depending, not only, on which chromosome is involved, but also on the position of breakpoints within the chromosome.

However, ring syndrome patients do not only display diverse symptoms resulting from deletions or duplications. Most of them have one feature in common. In a meta-study including more than two-hundred patients with congenital ring chromosomes it has been demonstrated that the majority of children with rings show a failure to thrive beyond the extent expected from their chromosomal imbalances[17]. It has been suggested that this is due to the mitotic instability of rings, preventing somatic cells to proliferate normally. The hypothesis is supported by the fact that growth failure is more common among patients with large ring chromosomes, than among those with small ones[17]. This is in accordance with the BFB model of ring chromosome dynamics. Statistically, large rings will undergo more SCEs per cell cycle than small rings and would thus have a higher propensity for breaking at anaphase. In a normal cell, this provokes a physiological DNA damage response leading to either cell cycle arrest or apoptosis[18].

From the reasoning above, it follows that a cell population carrying a ring chromosome would proliferate slower than a population without rings; the population with rings would be less fit and be at a selective disadvantage. Interestingly, ring chromosome loss or size reduction is not uncommon in cases with congenital rings. In particular, cases with small rings often exhibit a subclone without the ring chromosome and these patients are thus ring/monosomy mosaics[14]. In cases with large rings and prominent growth failure, heterogeneity of ring size is a more common feature. Children with ring chromosomes are thus illustrative examples of how natural selection at the cellular level may play a role for the symptoms and signs of human disease. However, many tumors show a pattern similar to that of normal cells. One might tentatively distinguish two main modes for chromosomal reorganisation in tumors: These are as type 1and 2.

Type 1: Where simple chromosome rearrangements lead to either the formation of a chimeric gene or a

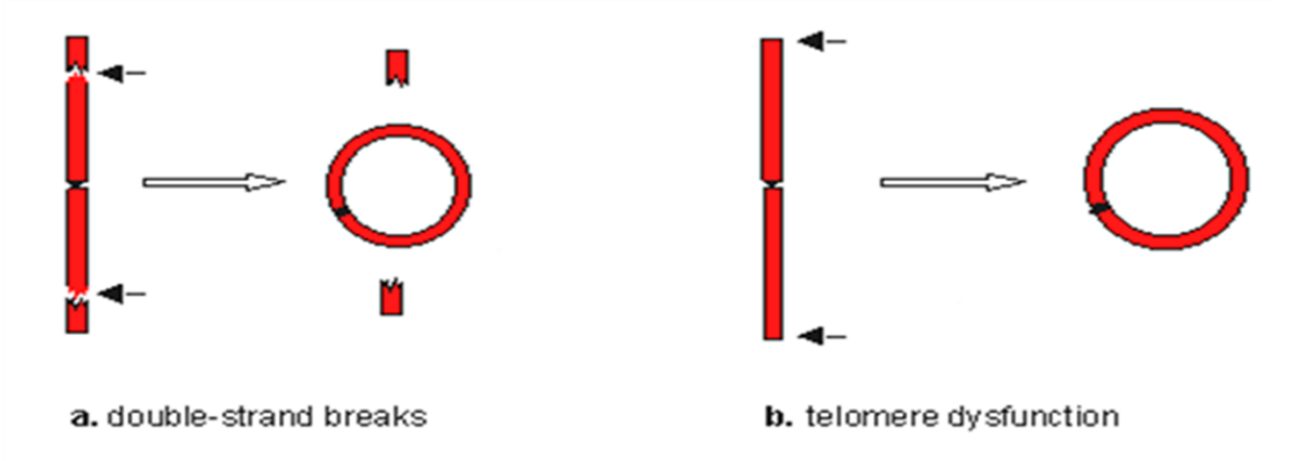

Figure 2. Ring chromosome formation may occur through breaks in the chromosome arms and fusion of the proximal broken ends, leading to loss of distal material (a). Rings may also be formed by telomere dysfunction triggering fusion of reactive chromosome ends without major loss of genetic material (b)

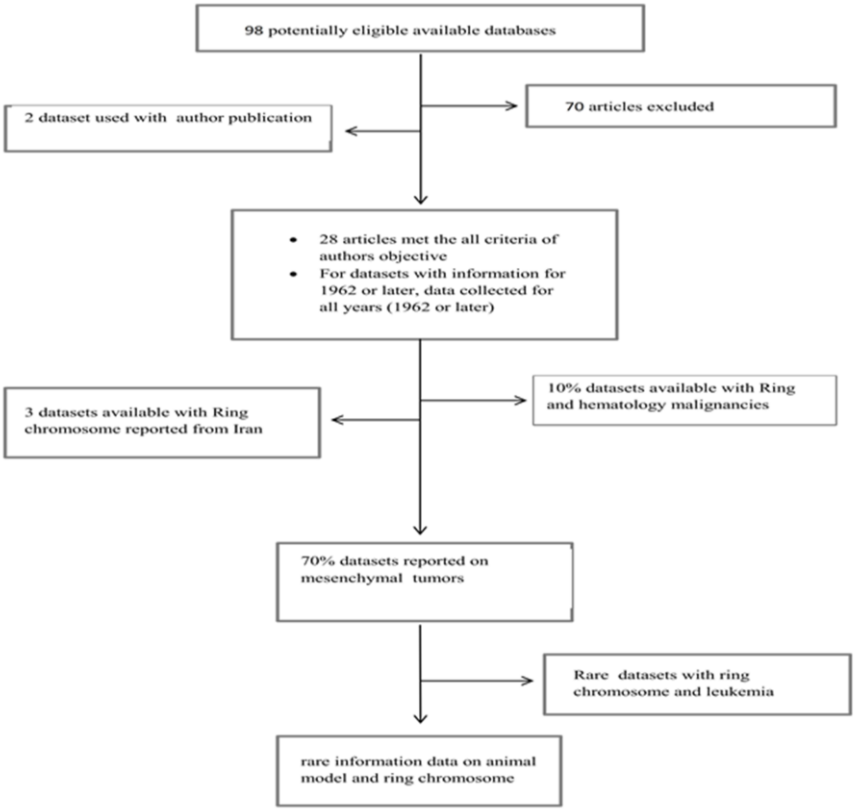

Figure 3. Database selection process.

deregulated oncogene expression with potent transforming capability. The BCR / ABLID: 1> fusion in chronic myeloid leukaemias and the EWS / FLI1 fusions in are examples of this mode. In general, such tumors show few additional chromosomal abnormalities and ring and dicentric chromosomes are

rare.

Type 2: Where vast chromosomal instability leads to formation of complex karyotypes and multiple gene changes including activation of oncogenes and loss of tumor suppresser genes. This mechanism of constant chromosome evolution most probably acts against a background of disrupted DNA damage and/or mitotic checkpoints 14. It is common in many aggressive solid tumors, e.g. lung cancer, ovarian carcinoma, pancreatic carcinoma, and a number of sarcomas.

In type 1 lesions and non-neoplastic cells, ring chromosome structure is relatively conserved: rings may be duplicated or lost, but structural rearrangements are rarely maintained in the cell population 8. In type 2 lesions, rings show extensive structural variability and provide a means for gene amplification. Ring chromosomes are thus illustrative proofs that chromosomal behavior is not only a function of straightforward molecular interactions; chromosomal topology and the physiological context in which a certain chromosome aberration occurs must also be taken into consideration.

Acquired Ring Chromosomes

Data was shown in table 1.

Discussion

The fusion of the short (p) and long (q) arms of a chromosome is referred to as a "ring chromosome". Ring chromosome disorders occur in approximately 1 in 50000-100000 patients. Ring chromosomes can result in birth defects, mental disabilities, and growth retardation if additional genes are deleted during the formation of the ring. Due to the severity of these large-scale aberrations affecting multiple contiguous genes, no possible therapeutic strategies for ring chromosome disorders have so far been proposed[20].

There are only two cases with ring chromosome 18 with different address reported from Iran[21-24]. Ring chromosomes are rare cytogenetic abnormalities that occur in less than 10% of hematopoietic malignancies but have been reported in up to 70% of mesenchymal tumors[2]. However, there are rare recurrent cytogenetic abnormalities in AML that have not been classified. This is primarily due to the small number of reported patients, whose risk category and response to treatment is not well known. In patients with hematopoietic malignancies, ring chromosomes are commonly part of a complex karyotype[5]. Ring chromosomes come to clinical attention either in association with developmental anomalies at the beginning of life or with telomere

Table 1: Ring chromosome prevalence (%) in human tumors*.

Hematological neoplasms	
Acute lympoblastic leukaemia	0.7
Chronic lymphocytic leukaemia	1.1
Acute myelogenous leukaemia	2.2
Chronic myelogenous leukaemia	1.0
Carcinomas	
Breast	5.7
Colon and rectum	4.6
Gallbladder	21.1
Kidney	13.0
Larynx	5.2
Liver	13.0
Lung	8.8
Mouth	1.9
Ovary	3.9
Pancreas	11.5
Prostate	0.0
Skin	3.7
Stomach	1.7
Thyroid	1.1
Uterine cervix	0.0
Urinary bladder	4.5
Uterus	2.2
Sarcomas	
Chondrosarcoma	5.6

Dermatofibrosarcoma protuberans	70.3
Ewing sarcoma	0.6
Leiomyosarcoma	11.2
Liposarcoma	21.1
Malignant fibrous histiocytoma	11.5
Mesothelioma	14.2
Osteosarcoma	12.2
Central nervous system tumours	
Astrocytoma	0.0
Glioma	0.0
Oligendroglioma	0.0
Meningioma	4.0

*Data from the Mitelman Database of Chromosome Aberrations in Cancer, October 4, 2001. http://cgap.nci.nih.gov/Chromosomes/Mitelman

shortening in ageing and neoplastic cells. It is likely that a transition from a DNA-damage sensitive to a DNA-damage tolerant state explains the high instability of rings in some tumor cells compared to those in non-neoplastic cells.

Rings are cytogenetic hallmarks that might be useful in determining a proper diagnosis [25-28]. The structure and formation of rings in tumors and leukaemias have been poorly investigated. The reason for this might be that acquired rings are often difficult to characterize by chromosome banding techniques owing to the complexity of rearrangements, suboptimal banding quality, and shortage of material. The cytogenetic delineation of ring chromosomes is further complicated by their structural instability[10,11].

Ring chromosomes occur when the two ends of a chromosome fuse together and form a ring shape. There are several ways in which this can occur. Breaks in the chromosome arms and fusion of the proximal broken ends can lead to ring formation with loss of distal chromosomal material. The cause of these DNA breaks and ligation of the ends is unknown. Alternatively, rings can be formed by telomere dysfunction. This occurs when the terminal ends of a chromosome fuse without significant loss of genetic material. Animal models and in vitro studies have shown that the mechanism of telomeric ring formation may be secondary to detachment of protective proteins on the chromosome ends when shortening of telomeric DNA occurs[2]. Guilherme RS *et al*, 2013[29,30] reported that data from the literature, supports the idea that ring chromosome patients fall into two groups: group one with (severe) clinical signs and symptoms due to the ring chromosome and group two with no obvious clinical problems apart from infertility[31,32].

Conclusion

Ring chromosomes are rare chromosomal aberrations, almost many times are of *de novo* origin, presenting a different phenotype regarding the loss of genetic material and genetic pattern instability. The karyotype represents the main analysis for detection of ring chromosomes, but other molecular tests are necessary for complete characterization. However, parental investigation is necessary for proper genetic counseling.

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Conflict of interest

The authors further declare that, they have no conflict of interest.

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