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Minireview

Chromosomal instability—mechanisms and consequences

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ABSTRACT

Chromosomal instability is defined as a state of numerical and/or structural chromosomal anomalies in cells. Numerous studies have documented the incidence of chromosomal instability, which acutely or chronically may lead to accelerated ageing (tissue-wide or even organismal), cancer or other genetic disorders. Potential mechanisms leading to the generation of chromosome-genome instability include erroneous/inefficient DNA repair, chromosome segregation defects, spindle assembly defects, DNA replication stress, telomere shortening/dysfunction — to name a few. Understanding the cellular and molecular mechanisms for chromosomal instability in various human cells and tissues will be useful in elucidating the cause for many age associated diseases including cancer. This approach holds a great promise for the cytogenetic assays not only for prognosis but also for diagnostic purposes in clinical settings. In this review, a multi-dimensional approach has been attempted to portray the complexity behind the incidence of chromosome-genome instability including evolutionary implications at the species level for some of the mechanisms of chromosomal instability.

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1. Chromosome instability

The fate of a cell with chromosomal abnormalities is inevitably death or in a less likely event cell transformation, and both of these events depend on the severity of aberrations. Cellular attrition contributes to ageing, while cell transformation potentially triggers cancer development processes. The causal relationship between chromosome aberrations and carcinogenesis was first revealed by Boveri as early as 1914 [1,2]. Currently, chromosome instability is a hallmark of cancer ensuing cell transformation events [3]. Chromosomal instability, if not the only trigger for carcinogenesis, is certainly demonstrated to accelerate the process in an overwhelming majority of cases [3,4]. Although somatic mutations are rampant in cancers, not all mutations lead to chromosome aberrations. Mutations in genes involved in genome surveillance

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mechanisms including DNA repair and tumour suppression have been demonstrated to be the major cause for a majority of hereditary and sporadic cancers [5,6]. Mutations may arise due to exposure to a wide variety of environmental carcinogens such as ultraviolet (UV) light, ionizing radiation and chemicals which produce a wide spectrum of DNA lesions. Even exposures to electronic waste have been shown to cause chromosomal aberrations among the clean-up workers of a dumping site in Jinghai, China [7]. Clearly, chromosome instability is emerging to be a central phenomenon, an inevitable end-point after all kind of exposures that inflict damage in nuclear and mitochondrial genomes.

2. Radiation-induced chromosome alterations

When it comes to radiation exposure, history has witnessed some grave acts of mankind and of nature: the merciless bombing of Hiroshima and Nagasaki (1945); tragic nuclear disasters — Chernobyl (1986); and acts of negligence and ignorance to rue over — Goiania (1987). Apart from this, we live in an environment where radiation-emitting devices are ubiquitous, and hence exposure to radiation is virtually inevitable. Thus, naturally there is an exigent need for understanding the biological consequences of different types of radiation, which might help in devising countermeasures against occupational or accidental exposure. There have been a few well-characterised cytogenetic studies on radiation exposed people in Chernobyl [8] and Goiania [9,10] which not only showed structural chromosomal aberrations soon after exposure but also their persistence several years after exposure. Chen et al. [11] reported that people living in the cities of Tokyo and Niigata, which are closer to the nuclear site at Fukushima, exhibited elevated levels of chromosomal aberrations of all sorts relative to a control group. We have analysed chromosomes from peripheral blood taken from workers of the Mayak nuclear facility, Russia, where they were occupationally exposed to either gamma rays, plutonium or both, many years ago. While simple chromosomal aberrations were significantly higher in the exposed groups as opposed to that in non-exposed controls, stable complex chromosomal aberrations and stable intrachromosomal aberrations were present almost exclusively among workers exposed to radioactive plutonium, but not those exposed to just gamma rays [12–14]. Examples of different types of chromosomal aberrations induced following exposure to ionising radiation in both humans and mice are shown in Fig. 1A–F.

Nuclear DNA is considered to be the primary target for ionizing radiation induced DNA damage and damage inflicted by radiation exposure can lead to chromosome- or chromatid- type aberrations depending on the nature and extent of DNA double strand breaks (DSBs) and cell cycle stage at the time of exposure [15]. Since translocations are clonal in nature and stable, they tend to persist even after several years, unlike dicentrics, whose numbers tend to decay with time due to mitotic death of dicentric bearing cells [16,17]. Repopulation of lymphocytes is also expected to dilute the frequency of dicentric chromosomes originally formed during the early times of radiation exposure. Cells with dicentrics may be eliminated from the lymphatic system with a time span of 6 months to a few years depending on the radiation dose and quality received [18]. In sharp contrast to unstable chromosome aberrations such as dicentrics, stable interchromosomal and intrachromosomal exchanges such as translocations and inversions have been shown to persist several years after exposure and such events have been found to be useful for retrospective biodosimetry [9].

The International Atomic Energy Agency has recommended the dicentric chromosome assay using peripheral blood lymphocytes for biodosimetry purposes in accidental radiation exposures [19]. Use of chromosomal aberration data in triage scenarios for dose estimation was effectively employed for the radiation accident in Goiania, Brazil [15]. Usefulness of the dicentric assay has also been validated by *in vivo* studies in mice [12,20,21]. Development of an automated platform for dicentric analysis is also in place for high throughput analysis of dicentrics in a radiological triage scenario [22,23].

3. Transgenerational effects of radiation

The underlying mechanisms leading to transgenerational effects of radiation are still unresolved. The first proposed mechanism was that radiation induces complex DNA double strand breaks that could result in persistent unresolved breaks during meiosis [24]. The recent notion is that sporadic epigenetic modification in the regions of repair leads to an unstable phenotype in the progeny [25,26]. A new study demonstrated the upregulation of a few miRNAs and maintenance of DNA methyltransferases, two days after radiation exposure, indicative of the initiation of genomic instability owing to epigenetic alterations ensuing transgenerational instability. Further studies are certainly warranted to clarify whether transgenerational effects are truly a radiation specific phenomenon [27]. The transgenerational effect, however, highly depends on the organism studied. Knowledge gained from studies on mice may not be directly applicable to humans owing to genomic complexity in the latter. A study on butterflies from Fukushima nuclear disaster site shows that the radiation exposure led to an accumulation of genetic damage as observed by abnormal traits getting propagated through generations, and also incidence of tumour formation in them [28]. Factors like the innate DNA repair dynamics, apoptotic death, organismal lifespan and regenerative capacity among others, all play a role in the differential outcome of radiation exposure on various species. The exact mechanisms of radiation-mediated transgenerational instability are basically poorly understood, and pose a crucial problem for the future; especially given that radiation exposures have become more frequent in the recent times.

Gardner et al. [29] hypothesised that the origin of leukaemia and lymphoma in young people near Sellafield nuclear plant in West Cumbria (U.K) could be due to parental exposure to radiation [30]. A study on children among the evacuees from the contaminated areas around Chernobyl revealed elevated levels of dicentric chromosomes in them with a dose estimate of up to 0.4 Gy [31] when compared to samples from unaffected regions. These findings suggest a strong possibility of transferring the residual genetic/epigenetic effects from the affected parents to their offspring [25,30,32–34]. Convincing evidence of the phenomenon in humans however was obtained by comparing microsatellite profiles of parents exposed to ^{137}Cs radiation at Chernobyl and those of their progeny 19 years after the radiation exposure [35]. Since stable chromosomal aberrations tend to persist in the genome, such aberrations in germ cells would mean transfer of such abnormalities to the progeny. However, the outcome of such expressions could be governed by epigenetic control over the locus too. As such, much on the mechanisms behind transgenerational effects of radiation remains to be uncovered.

4. Chemical exposures and chromosomal aberrations

Disposal of toxic waste from industrial sources to water and soil considerably increases the health risks for plants, animals and humans. Accidental or occupational exposure to a variety of chemicals could induce mutations in genome surveillance genes. While such mutations in somatic cells could increase risk of cancer, those in germ cells could lead to hereditary disorders. One of the worst