Available online at www.sciencedirect.com
ScienceDirect
Toxicology Letters 166 (2006) 1–10
Toxicology Letters
www.elsevier.com/locate/toxlet

Mini-review

Number of centromeric signals in micronuclei and mechanisms of aneuploidy

G. Iarmarcovai *, A. Botta, T. Orsière

Laboratoire de Biogénotoxicologie et Mutagenèse Environnementale (EA 1784; IFR PMSE 112), Faculté de Médecine, Université de la Méditerranée, 27 Bd Jean Moulin, 13385 Marseille Cedex 5, France

Received 19 April 2006; received in revised form 29 May 2006; accepted 30 May 2006
Available online 6 June 2006

Abstract

Genome instability or changes in chromosome structure and number are important facets of oncogenesis. Aneuploidy is a major cause of human reproductive failure and plays a large role in cancer. It is therefore important that any increase in its frequency due to occupational exposure to mutagens and carcinogens should be recognized and controlled. In recent years, the cytokinesis-block micronucleus assay has emerged as a biomarker of chromosome/genome damage relevant to cancer. Fluorescent in situ hybridisation using human pancentromeric DNA probes discriminates between the presence of acentric chromosomal fragments and whole chromosomes in binucleated micronucleated lymphocytes. The separated analysis of centromeric micronuclei may improve the sensitivity of the micronucleus assay in detecting genotoxic effects and chromosome instability. Our previous findings suggest that aneugenic events leading to micronuclei (MN) containing a single centromere (C1 + MN) and two or more centromeres (Cx + MN) may arise through different pathways. Chromosome migration impairment would lead to increased C1 + MN frequency whereas centrosome amplification would induce Cx + MN with three or more centromeric signals. Additional studies that target cellular defects on the centrosome (microtubule nucleation, organization of the spindle poles, cell cycle progression) are required to better understand aneuploid cell production.

Keywords: Cytokinesis-block micronucleus assay; Fluorescent in situ hybridisation; Chromosome loss; Chromosome instability; Centrosome

Contents

* Corresponding author. Tel.: +33 4 91 32 45 48; fax: +33 4 91 32 45 72.
E-mail address: Gwenaelle.Iarmarcovai@medecine.univ-mrs.fr (G. Iarmarcovai).

0378-4274/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.toxlet.2006.05.015

1. Introduction

Genome instability or changes in chromosome structure and number are important facets of oncogenesis (Saunders et al., 2000). Genome instability in human cancers can be divided into microsatellite instability (MIN), which is usually equated with DNA polymerase errors, and chromosome instability (CIN), which can result from errors in chromosome partitioning. Mutation in DNA mismatch repair genes leads to the accumulation of point mutations in the DNA sequence, which are readily observed in microsatellites, short DNA repeat sequences dispersed throughout the genome. MIN tumours are distinguished from other tumours by their apparently normal karyotype (i.e. normal complement and structure of chromosomes). The vast majority of tumours, however, exhibit abnormal karyotypes (CIN) involving either chromosomal rearrangement and/or aneuploidy (Fenech, 2002). Changes in chromosome structure are due to errors in DNA metabolism, repair, recombination or other rearrangements of the DNA sequence, misregulation of the cell cycle, disruption of the mitotic spindle apparatus, and centrosomal duplication (Saunders et al., 2000). Abnormalities of centrosome integrity and mitotic spindle apparatus may therefore play a role in the onset of neoplasia (Yuen et al., 2005).

The molecular mechanisms ensuring accurate chromosome segregation during mitosis are critical to the conservation of euploidy in eukaryotic cells (Yuen et al., 2005). In this respect, numerous mechanisms could consequentially destabilize chromosomes, including loss of mitotic checkpoint function, abnormal amplification of centrosome, defects in the kinetochore-microtubule attachment, and movement of chromosome relative to the pole (Saunders et al., 2000; Fukasawa, 2005). Errors in this process result in unequal segregation of the chromosomes at cell division, in numerical chromosomal changes, and in the production of aneuploid cells (i.e. cells in which the chromosome number is not a multiple of the haploid number of the species) (Ochi, 2002).

Aneuploidy can be detected through traditional metaphase cytogenetics, interphase cytogenetics (fluorescent in situ hybridisation (FISH), multicolour FISH, spectral karyotyping, and comparative genomic hybridisation techniques), flow cytometry, and image cytometry (Dey, 2004). Cytogenetic biomarkers such as chromosome aberrations and micronuclei (MN) are, however, the most frequently used endpoints in human population studies. They are sensitive in measuring exposure to genotoxic agents and are early predictors of cancer risk (Bonassi et al., 2005). Population studies using chromosomal aberration analysis and the cytokinesis-blocked micronucleus (CBMN) assay serve to investigate occupational exposure, environmental pollution, diet, dietary supplementation, lifestyle, and clinical purposes such as sensitivity to anticancer chemotherapy, pharmaceutical treatment, or groups of patients (Bonassi et al., 2005). Applying FISH of centromeric DNA probes to the CBMN assay enables one to discriminate between chromosome breakage and chromosome loss, coming from either impairments in chromosome migration or non-disjunction (Migliore et al., 1993; Norppa et al., 1993).

2. Aneuploidy and chromosome instability

2.1. Origins of aneuploidy: aneugens

Aneugens are defined as agents that affect cell division and the mitotic spindle apparatus, resulting in the loss or gain of whole chromosome, thereby inducing aneuploidy. Bolt et al. (2004) reported that the classification