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PROSPECTS

Aneuploidy and Cancer

Ya-Hui Chi and Kuan-Teh Jeang*

Molecular Virology Section, Laboratory of Molecular Microbiology, The National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892-0460

Abstract The cell's euploid status is influenced by, amongst other mechanisms, an intact spindle assembly checkpoint (SAC), an accurate centrosome cycle, and proper cytokinesis. Studies in mammalian cells suggest that dysregulated SAC function, centrosome cycle, and cytokinesis can all contribute significantly to aneuploidy. Of interest, human cancers are frequently aneuploid and show altered expression in SAC genes. The SAC is a multi-protein complex that monitors against mis-segregation of sister chromatids. Several recent experimental mouse models have suggested a link between weakened SAC and in vivo tumorigenesis. Here, we review in brief some mechanisms which contribute to cellular aneuploidy and offer a perspective on the relationship between aneuploidy and human cancers. J. Cell. Biochem. 102: 531–538, 2007.

Key words: aneuploidy; cancer; spindle assembly checkpoint; mitosis; cytokinesis; centrosome

Humans have 23 pairs of diploid chromosomes. Aneuploidy in somatic human cells arises whenever the number of chromosomes deviates from 46. Several human genetic diseases exhibit aneuploidy. Common examples include Down syndrome which has trisomy 21, or Turner syndrome with monosomy in sex chromosome X.

Distinct species have different numbers of chromosomes with genomes which are not always diploid. While mammals are diploid, other genomes hold triploid (3N) and tetraploid (4N) (such as catfish, cyprinids and carp) or hexaploid (6N) (such as wheat) examples. Chromosomes numbers also do not relate directly to presumed positions in the evolutionary hierarchy. For example, humans have 46 chromosomes, but apes (Pan troglodytes) have 48 chromosomes; goats (Capra hircus) have 60 chromosomes; and dogs (Canis familiaris) have 78 chromosomes (see http://morgan.rutgers.edu/morganwebframes/level1/page2/ChromNum.html). A comparison of human and chimpanzee genomes reveals that human chromosome 2 was derived from two smaller chromosomes found in great apes (chromosomes 2A and 2B), suggesting that humans may have lost a chromosome due to translocation some time over the past six million years [Kehrer-Sawatzki and Cooper, 2007]. Indeed, extant evidence shows that gains or losses of chromosomes occur naturally during the course of evolution.

However, in non-evolutionary time scale (e.g., within a single human life span), gains or losses of chromosomes (i.e., aneuploidy) usually manifest in diseases. Unlike point mutations which may affect only a handful of genes, wholesale changes in chromosome number alter dramatically (e.g., one single human chromosome approximates 5% of the entire human genome) the landscape of gene expression. Some investigators have suggested that such large modulations in gene expression by themselves may sufficiently induce transformation [Boveri, 1902; Duesberg and Li, 2003]. Accordingly, aneuploidy has been reported as a hallmark of many malignancies [Rajagopalan and Lengauer, 2004]. Nonetheless, currently it remains contested whether aneuploidy is causal of cancers or simply reflects consequential changes in cells after they have become transformed [Rajagopalan and Lengauer, 2004; Duesberg et al., 2005; Yuen et al., 2005].

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*Correspondence to: Kuan-Teh Jeang, Building 4, Room 306, 9000 Rockville Pike, Bethesda, MD 20892-0460.
E-mail: kj7e@nih.gov

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SEVERAL ROADS LEAD TO ANEUPLOIDY

During mitosis, a mammalian cell needs to segregate with fidelity her duplicated chromosomes into two daughter cells. Aneuploidy can surface in various ways (Fig. 1) during DNA division including via (1) improper attachments of chromosomes to the mitotic spindles, (2) failed cytokinesis, and (3) abnormal numbers of mitotic spindle poles.

Improper Microtubule Attachment and the Spindle Assembly Checkpoint (SAC)

To ensure fidelity of segregation, duplicated chromatids must attach with equal tension to bipolar mitotic spindles. A spindle assembly checkpoint (SAC) exists in cells to monitor this proper attachment. The SAC was initially characterized by screening yeast *Saccharomyces cerevisiae* for genes required to arrest cells in response to microtubule toxins [Hoyt et al., 1991]. Two groups of proteins, mitotic arrest deficient (MAD, including MAD1, MAD2, and MAD3) and budding uninhibited by benzimidazole (BUB, including BUB1, BUB2, and BUB3) emerged from such assays (Fig. 2). During mitosis, these SAC genes/proteins serve monitoring functions at kinetochores which are structures that consist of centromere DNA complexed with more than 100 proteins [Cleveland et al., 2003].

In principle, loss of SAC function should increase ambient prevalence of aneuploidy. Several recent knock out mouse models have been constructed to test this hypothesis and its significance for cancer. Unfortunately, because

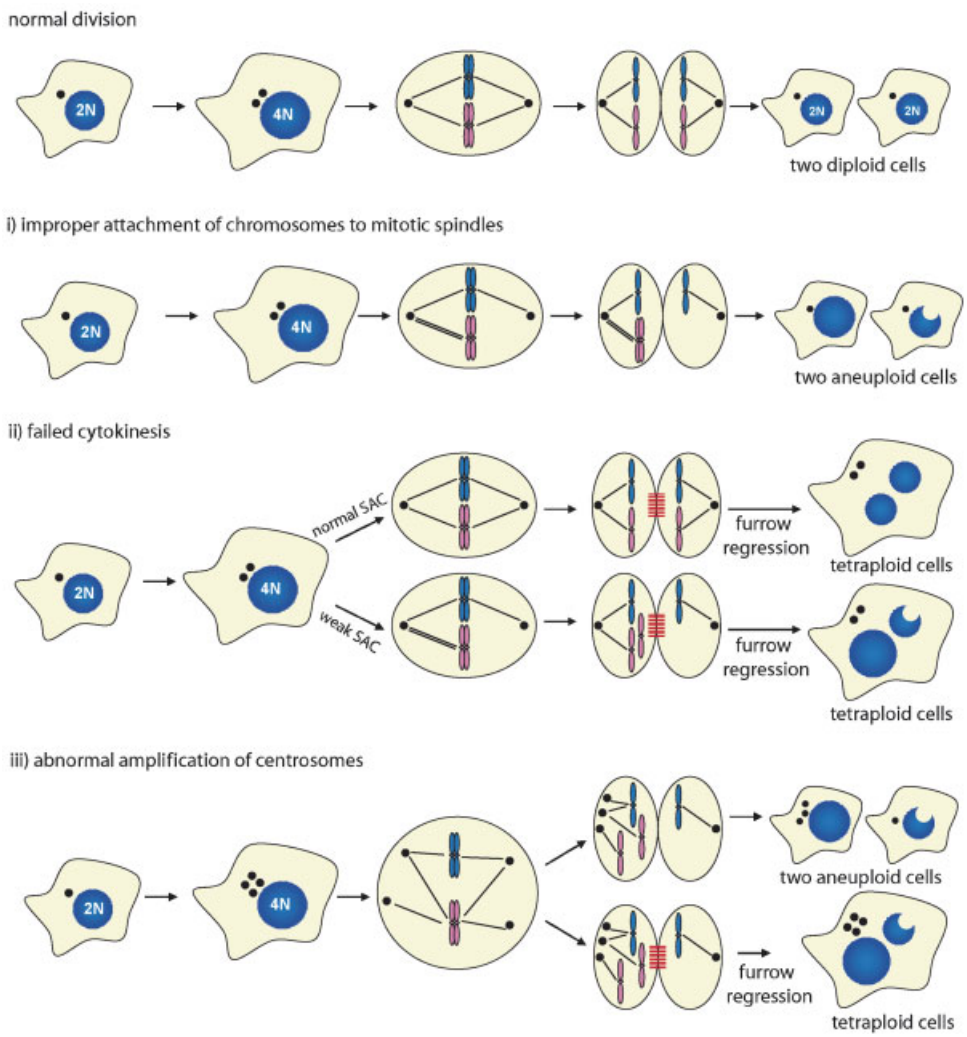

Fig. 1. Pathways to aneuploidy. Aneuploidy can be contributed from (i) improper attachment of chromosomes to mitotic spindles; (ii) failed cytokinesis; (iii) abnormal amplification of centrosomes. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

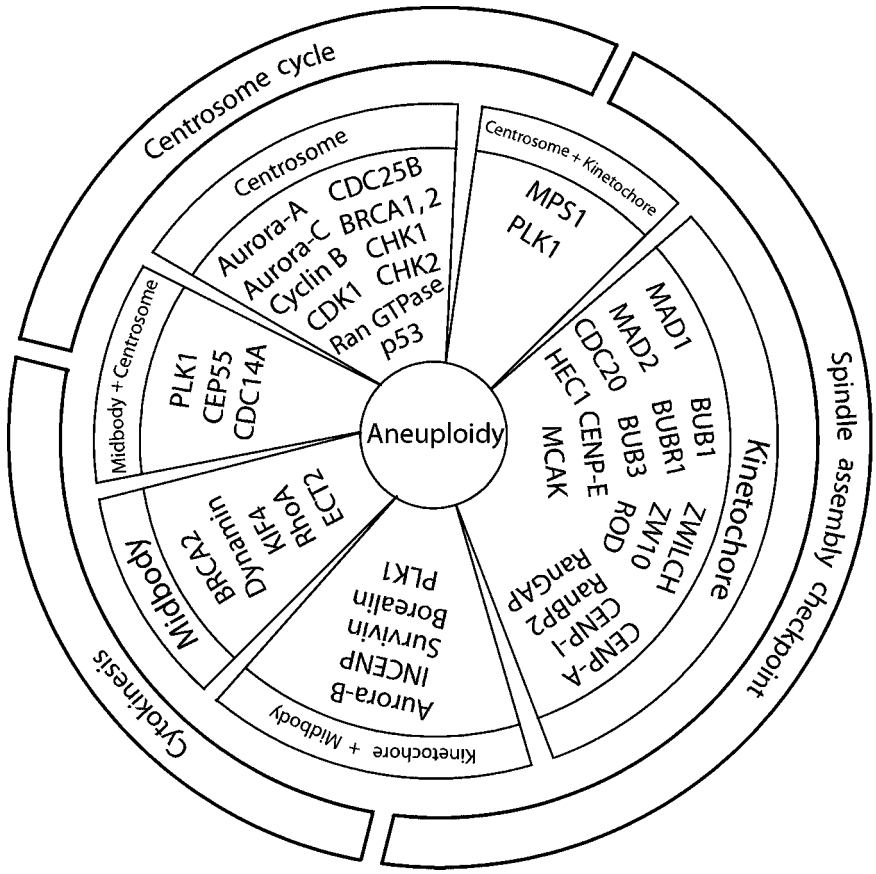

Fig. 2. Aneuploidy associated genes. The figure shows a non-exhaustive listing of some of the genes that have been reported to be involved in different mechanisms associated with aneuploidy.

SAC proteins apparently serve more than purely checkpoint function, results from knock out of these genes in mice have been challenging to interpret. For instance, homozygous loss of SAC proteins in mice generally emanates with embryonic lethality, and live births of $Mad1^{-/-}$, $Mad2^{-/-}$, $BubR1^{-/-}$, or $Bub3^{-/-}$ mice have not been achieved [Kalitsis et al., 2000; Michel et al., 2001; Dai et al., 2004; Iwanaga et al., 2007]. However, heterozygous knock out mice with partial loss of SAC function can be secured and studied (Table I). Accordingly, a higher than normal rate (25%) of $Mad2^{\pm}$ (Table I) mice was found to develop lung adenocarcinoma by 18–19 months of age [Michel et al., 2001], and deliberate overexpression of Mad2 in transgenic mice (which likely leads also to loss of function) yielded a wide variety of neoplasias [Sotillo et al., 2007]. Concordant findings were verified when the Mad2-related check point protein Mad1 was heterozygously reduced. Thus, 19% of $Mad1^{\pm}$ (Table I) mice developed constitutive tumors in various organs, including lung adenocarcinoma, hepatocellular carcinoma, osteosarcoma, uterine sarcoma, and rare spontaneous tumors such as rhabdomyosarcoma and hemangiosarcoma [Iwanaga et al., 2007]. Similarly, $BubR1^{\pm}$ (Table I) mice when exposed to carcinogens were found to be more predisposed than comparably-exposed $BubR1^{+/+}$ mice to develop early lung and colon adenocarcinomas [Dai et al., 2004]. Finally, $CENP\text{-}E^{\pm}$ (Table I) mice were also seen to exhibit increased frequency of spontaneous lymphomas and lung tumors by 19–21 months of age. Unexpectedly, treatment with chemical tumor inducers inhibited rather than enhanced tumorigenesis in $CENP\text{-}E^{\pm}$ mice [Weaver et al., 2007]. Thus, depending on genetic context, induction of "mild" aneuploidy may predispose cells to transformation, while creation of more "extreme" aneuploidy could trigger cell death and manifest with an overall apparent dampening of oncogenesis.

Biochemical findings at the cellular level support a link between weakened SAC (Fig. 2)

TABLE I. Tumor Outcomes in Mouse SAC Knock Out Models

Gene	Aneuploidy detectable in MEF?	Susceptible to spontaneous cancer?	Chemical treatments increase tumor incidence?	MEFs induce tumors in nude mice?
Mad1$^{\pm}$	Yes	Yes (lymphoma, carcinoma, sarcoma, and adenoma in various organs)	Nocodazole; yes	Yes
Mad2$^{\pm}$	Yes	Yes (lung adenocarcinoma)	ND	Yes
Mad2 overexpression	Yes	Yes (lymphoma, carcinoma, sarcoma and adenoma in various organs)	ND	ND
BubR1$^{\pm}$	Yes	No	Azoxymethane (AOM); yes	No
BubR1$^{\pm}$*Apc*$^{Min/+}$	Yes	Increase in colon cancer but decrease in small intestine adenoma compared to *Apc*$^{Min/+}$ mice	ND	ND
BubR1$^{H/H}$	Yes	No	ND	ND
Bub3$^{\pm}$	Yes	No	DMBA; yes	No
Bub3$^{\pm}$*Rae1*$^{\pm}$	Yes	No	DMBA; yes	ND
Rae1$^{\pm}$	Yes	No	DMBA; yes	ND
Bub3$^{\pm}$*Trp53*$^{\pm}$	ND	No	ND	ND
Bub3$^{\pm}$*Rb1*$^{\pm}$	ND	No	ND	ND
CENP-E$^{\pm}$	Yes	Yes (lymphoma and lung tumor)	DMBA; no (DMBA treatment decreased tumor incidence)	ND
CENP-E$^{\pm}$*p19/ARF*$^{-/-}$	Yes	Yes, however, *CENP-E*$^{\pm}$ delays tumorigenesis in *p19/ARF*$^{-/-}$ mice	ND	Yes
CENP-E$^{\pm}$expressing SV40 large T antigen	Yes	ND	ND	Yes

and aneuploidy [Yuen et al., 2005; Haller et al., 2006; Iwanaga et al., 2007]. For example, mouse embryonic fibroblasts (MEFs) heterozygously inactivated for a single *Mad1*, *Mad2*, *BubR1*, *CENP-E*, or *Bub3* allele show higher than normal proclivity for developing aneuploidy [Kalitsis et al., 2000; Michel et al., 2001; Dai et al., 2004; Iwanaga et al., 2007; Weaver et al., 2007]. Using RNA interference-mediated knock down, Meraldi et al. [2004] found that cells diminished for MAD2 or BUBR1 could progress into anaphase despite incomplete attachment of chromosomes to bilateral spindle poles. Similarly, cells with reduced MAD1 or MAD2 function become more tolerant of nocodazole-induced mitotic arrest with resulting aneuploidy than wild type cells [Kienitz et al., 2005]. Additional studies have shown that reduced BUB1 or CENP-E function [Weaver et al., 2003] also increases cellular aneuploidy. Taken together, these findings are consistent with an important censoring role served by the SAC in preserving euploidy.

Failed Cytokinesis and Genomic Stability

When mitosis nears completion and sister chromatids reach defined positions, a contractile ring forms in the cell's cortex midway between the parted chromosomes and divides the mother cell into two daughters. This process of cytokinesis is the final step that consummates cell division. If cytokinesis fails, cells with unstable tetraploidy are produced (Fig. 1). In many cases, these tetraploid cells transit later to aneuploidy.

A recent report from Shi and King [2005] suggests that cells with spontaneous chromosome non-disjunction in mitosis incur bi-nucleated tetraploid states (Fig. 1). Surprisingly, the rate of mis-segregation in these bi-nucleated cells in the next cell cycle is 166-fold higher than otherwise mono-nucleated cells. Although some of the findings in this study have been contested [Weaver et al., 2006], one interpretation from the results suggests that unstable bi-nucleated tetraploid cells arising from failed cytokinesis provide a significant precursor population that develops into more stable aneuploid mononuclear progenies. If this reasoning is correct, such mechanism provides a route whereby improper cytokinesis engenders aneuploid genomes.

Aberrant Centrosomes and Multi-Polar Mitosis in Cancers

Interphase centrosomes are organelles that form the mitotic spindle poles. Centrosomes are composed of two orthogonally arranged centrioles surrounded by amorphous masses of pericentriolar material (PCM). The PCM contains proteins responsible for microtubule nucleation and anchoring including γ-tubulin, pericentrin, and ninein. Centrosomes undergo duplication precisely once during S phase, and duplication of the centrosome is coupled to DNA replication. In particular, the activation of cyclin E-CDK2 (cyclin-dependent kinase 2) complex at the G1/S phase transition of the cell cycle allows both DNA replication and centrosome duplication to proceed. During mitosis, the two centrosomes develop into respective bipolar poles of the mitotic spindles (Fig. 1), apparatuses which anchor accurate chromosome segregation.

Several cellular proteins, including p53, BRCA1, CHK1, CHK2, Ran GTPase, Aurora A, PLK1, Cyclin B1, and CDK1 (Fig. 2), regulate centrosome duplication and function [Kramer et al., 2004]. If not properly regulated, abnormal centrosome numbers (fewer or greater than two centrosomes in mitosis) can arise which would incite chromosome segregation errors (Fig. 1). For example, select mutations in Aurora kinase impede centrosome separation and lead to formation of a monopolar spindle [Glover et al., 1995]. On the other hand, in other settings, over-expression of Aurora A creates over-amplification of centrosomes and multipolar mitosis leading to cellular aneuploidy and transformation [Zhou et al., 1998]. There is also evidence that p53 and breast cancer susceptible gene, BRCA2, also act to regulate centrosome numbers [Fukasawa et al., 1996; Nakanishi et al., 2007; Shinmura et al., 2007].

Boveri [1914] described cancer cells with frequent amplification of centrosomes and postulated that changes in centrosome functions may be key to cancer formation. Over time, this description has been verified; and today, it is widely held that aberrant centrosome numbers are prevalent in many types of cancers including breast, lung, bone, pancreas, colorectal, prostate, head, and neck [Saunders, 2005]. Remarkably, ~80% of breast cancers exhibit amplified centrosomes [Lingle et al., 2002]. Moreover, the incidence of centrosome defects increases with the higher histological grade of carcinomas. Hence, the frequency of centrosome amplification in cervical carcinomas rises from nearly zero in normal epithelium, to ~20% of cells from grade one tumors, ~50% in grade two tumors, and nearly 70% in grade three tumors [Pihan et al., 2003]. While not formally conclusive, this correlation could be interpreted to support a causal relationship between centrosome defect and carcinogenesis.

TRANSFORMING VIRUSES AND CELLULAR ANEUPLOIDY

While the etiologies of many spontaneous cancers are incompletely understood, viral infections are clear causes of several well-defined human malignancies. Examples include hepatocellular carcinomas and Hepatitis B virus (HBV)/Hepatitis C virus (HCV) [Bruix et al., 2006], cervical cancers and human papilloma virus (HPV) [Woodman et al., 2007], Burkitt's lymphoma and Epstein-Barr virus (EBV) [Pattle and Farrell, 2006], Adult T-cell leukemia (ATL) and human T-cell leukemia virus type 1 (HTLV-1) [Grassmann et al., 2005; Takatsuki, 2005], and Kaposi's sarcoma and HHV8 infection [Levy, 1995]. If aneuploidy is a route to cellular transformation, then investigating how cancer viruses create chromosomal instability in initiating cellular transformation should be informative.

There is evidence that transforming viruses target both the SAC checkpoint and the mitotic spindle poles. Studies have found that HTLV-1 encodes an oncoprotein Tax which inactivates the SAC [Jin et al., 1998; Kasai et al., 2002] and creates both centrosome over-duplication [Ching et al., 2006] and centrosome fragmentation [Peloponese et al., 2005; Afonso et al., 2007]. Consistent with these findings, ATL cells which arise from HTLV-1 infection are highly aneuploid and show morphologically distorted multi-lobulated nuclei characteristic of 'flower cells' [Matsuoka, 2005; Matsuoka and Jeang, 2007].

Data from HPV and EBV also correlate the development of aneuploidy with transformation. Abnormal multi-polar mitoses in suprabasal epithelial layers of tissues have long been recognized as a hallmark of high-risk HPV-associated lesions of the uterine cervix. Here, aberrant mitotic spindle pole formation resulting from supernumerary centrosomes is

considered to explain this finding. Interestingly, persistent over-expression of HPV16 E6 and E7 oncoproteins likely incurs the emergence of numerical centrosome abnormalities, multi-nuclei, micronuclei, and large multi-lobulated nuclei, all features commonly seen in cervical cancer specimen [Duensing et al., 2000; Duensing and Munger, 2004].

Unscheduled mitotic progression and subsequent polyploidy and/or micro-nuclei formation are also seen in EBV-associated Burkitt's lymphoma. Latent EBV infection can compromise the SAC and provide anti-apoptotic function that protects cells from caspase-induced cell death [Leao et al., 2007].

TUMOR SUPPRESSORS AND ANEUPLOIDY

Cancer development has been attributed in part to the loss of tumor suppressor functions. There are suggestions that development of aneuploidy can also arise from inactivation of tumor suppressor proteins. First, the loss of p53 function has been described to give rise to spontaneously tetraploid cells [Livingstone et al., 1992]. For instance, Fujiwara et al. [2005] reported that p53-null ($p53^{-/-}$) cells are genetically unstable and produce tetraploid cells which are tumorigenic. Second, abnormal cytokinesis was observed in cells deficient in breast cancer susceptible gene, BRCA2 [Daniels et al., 2004]. BRCA2-deficient cells accumulate chromosome contents of 4N and greater after successive passages. Given the relationship between tetraploidization and aneuploidization, a significant number of tetraploid p53 and BRCA2 deficient cells are likely to progress into aneuploidy.

ANEUPLOIDY AND HUMAN CANCERS

Over 100 years ago, von Hansemann [1890] first described the observation of aneuploidy in malignant tumors. More recently, it has been suggested that the degree of aneuploidy in cells reflects well the cell's proclivity for genomic instability [Duesberg et al., 1998]. In support of a role for aneuploidy in cancer causation, certain non-mutagenic carcinogens, such as asbestos, appear to transform cells by creating chromosomal mis-segregation and aneuploidy without causing DNA structural aberrations [Moyer et al., 1994]. Thus while DNA mutations may explain some cancers, it has been raised that in other malignancies an imbalance in the dosage of thousands of normal genes caused by chromosomal gains or losses may be a separately independent contributor to carcinogenesis. Interpretations of several recent studies appear to provide support for a link between chromosome mis-segregation and aneuploidy with cellular transformation [Fukasawa, 2005; Shi and King, 2005].

Despite the above reasoning, direct evidence that conclusively connects aneuploidy to human cancers is still evolving. First, there is increasing evidence that mutations in SAC genes or deregulated expression of SAC proteins contribute to the development of human cancers [Yuen et al., 2005; Weaver and Cleveland, 2006; de Carcer et al., 2007]. Interestingly, consistent with results from mouse models [Michel et al., 2001; Iwanaga et al., 2007], up to 40% of human lung cancer cells have been found to carry defects in mitotic checkpoint genes, including changes in MAD1 and MAD2 [Takahashi et al., 1999; Coe et al., 2006]. Second, a surprising connection was recently established between individuals who develop frequent childhood cancers [Hanks et al., 2004; Matsuura et al., 2006], such as rhabdomyosarcoma and leukemia, and the SAC that guards against aneuploidy. Thus, Hanks et al. [2004] characterized such individuals who have a rare genetic phenotype, mosaic variegated aneuploidy, in which $>25\%$ of cells in the body develop aneuploidy. These investigators found that this genetic phenotype is explained by mutation of both alleles for the SAC-related protein BUB1B (i.e., BUBR1). Third, Barrett's esophagus (BE)-associated polyploid dysplasia is a known precursor for esophageal adenocarcinoma [Thurberg et al., 1999]. DNA aneuploidy in BE can be used as confirmatory biomarker for identification of dysplasia. Because dysplasia precedes frank malignancy, aneuploidy in BE suggests that disorder in chromosome numbers leads to, rather than follow after, the development of cancerous malignancies. Taken together, the accumulating evidence is increasingly compatible with a causal connection between aneuploidy and manifestation of human cancers.

CONCLUDING REMARKS

The emergence of cancer could be viewed as a deleterious byproduct of an evolutionary process driven to select for genetic diversity

through gains and losses in chromosome numbers and gene mutations. Aneuploidy may contribute positively to speciation and negatively to the development of pathological neoplasms. By understanding the normal processes of cell division and the checks that guard against genomic aberrations, one can understand better proteins whose dysfunction gives rise to aneuploidy. Such proteins may be useful targets for cancer chemotherapy.

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