

---

# CINcere Modelling: *What Have Mouse Models for Chromosome Instability Taught Us?*

Judith E. Simon, Bjorn Bakker and Floris Foijer

---

## Abstract

Chromosomal instability (CIN) is a process leading to errors in chromosome segregation and results in aneuploidy, a state in which cells have an abnormal number of chromosomes. CIN is a hallmark of cancer, and furthermore linked to ageing and age-related diseases such as Alzheimer's. Various mouse models have been developed to explore the role of CIN in ageing and cancer. While these models reveal only a modest contribution of CIN to the initiation of cancer, they also clearly show that CIN is a powerful accelerator of cancer in a predisposed background. Other than cancer, CIN also appears to provoke premature ageing in some of the CIN models. In this review, we discuss the phenotypes of the various available mouse models, what we have learnt so far, and importantly, also which questions still need to be addressed.

---

## Keywords

Aneuploidy · Chromosomal instability · Cancer · Ageing · Mouse models

## Contents

1	Chromosomal Instability and Aneuploidy.....	40
2	Provoking CIN In Vivo.....	41

---

Judith E. Simon and Bjorn Bakker contributed equally to this chapter

---

J.E. Simon · B. Bakker · F. Foijer (✉)  
European Research Institute for the Biology of Ageing (ERIBA),  
University Medical Center Groningen, University of Groningen,  
A. Deusinglaan 1, 9713 AV Groningen, The Netherlands  
e-mail: f.foijer@umcg.nl

3	In Vivo Consequences of CIN .....	42
4	Can CIN Initiate Cancer? .....	43
5	Does CIN Predispose to Cancer? .....	43
6	Which Genes Collaborate with CIN in Cancer? .....	49
7	CIN as a Tumour Suppressor .....	49
8	What Other Phenotypes Are Provoked by CIN? .....	50
9	Linking Ageing and CIN In Vivo .....	50
10	What Have We Learnt from Modelling CIN in the Mouse so Far? .....	51
11	Questions that Need to Be Addressed .....	52
11.1	Which Mutations Make an Aneuploid Cell an Aneuploid Cancer Cell? .....	52
11.2	At What Rate Is CIN Tumorigenic and at What Levels Tumour Suppressive? .....	52
11.3	What Determines the Tissue Specific Response to CIN? .....	53
11.4	What Are the Molecular Mechanisms that Explain the Link Between CIN and Ageing? .....	53
11.5	What Is the Potential of CIN-Targeting Therapy? .....	54
	References .....	55

---

# 1 Chromosomal Instability and Aneuploidy

During each cell division our genetic code is replicated, followed by symmetrical segregation of all chromosomes into the emerging daughter cells. Cancer cells occasionally exhibit errors segregating their chromosomes, a process known as chromosomal instability (CIN), leading to cells with abnormal numbers of chromosomes, a state defined as aneuploid. In addition to whole chromosome abnormalities, CIN can also lead to structural abnormalities such as amplifications, deletions or translocations, either through defects in the DNA damage machinery or as a direct result of chromosome missegregation events (Janssen et al. 2011). Although numerical and structural abnormalities frequently coincide, in this review we will focus on how mouse models have contributed to our understanding of the consequences of whole chromosome instability.

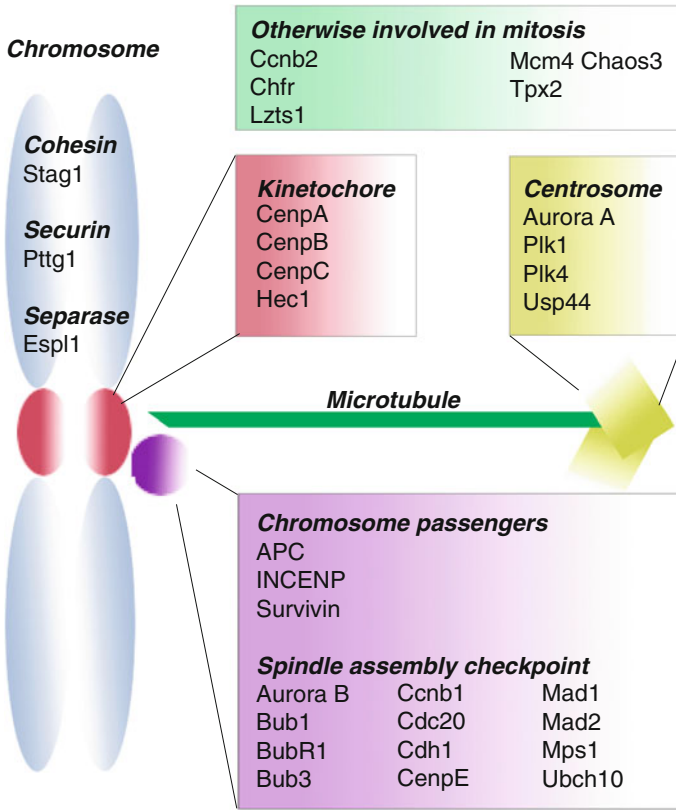
David von Hansemann was the first to report abnormal chromosome numbers in carcinoma samples in 1890, long before the relationship between chromosomes and the genetic code had been established (Hardy and Zacharias 2005; Bignold et al. 2006; Siegel and Amon 2012). Early in the 20th century, Theodor Boveri showed that aneuploidy leads to abnormal development or even death by injecting two sperms instead of one into sea urchin embryos. These observations led to the hypothesis that aneuploidy can lead to cancer or developmental defects (Boveri and Manchester 1995; Bignold et al. 2006; Boveri 2008, Ried 2009). Since then, many studies confirmed that CIN is a hallmark of human malignancies, affecting 2 out of 3 cancers (Duijf et al. 2013). More recently, aneuploidy has also been associated with ageing and age-related diseases (Faggioli et al. 2012). For instance, trisomy for chromosome 21 is frequently found in plaques in Alzheimer patients’ brains (Iourov et al. 2009). Conversely, people with Down syndrome develop early onset Alzheimer’s disease (Lai and Williams 1989), further emphasizing the relationship between trisomy 21 and neurodegenerative disease.

Although CIN has been associated with cancer for more than a century, we are only beginning to understand the consequences of CIN and aneuploidy at the cellular and molecular level. CIN is believed to accelerate the evolution of cancer cells by facilitating gain of oncogenes and loss of tumour suppressor genes. Paradoxically, when modelled in yeast strains (Torres et al. 2007) or mouse embryonic fibroblasts (MEFs) (Williams et al. 2008), aneuploidy appears to decrease rather than increase cell proliferation, suggesting that cancer cells find ways to cope with the adverse effects of aneuploidy. However, as transformation of aneuploid cells into aneuploid cancer cells can only occur in vivo by definition, animal models for CIN are essential to solve this paradox.

---

## 2 Provoking CIN In Vivo

Several processes that safeguard correct chromosome segregation have been targeted to engineer mouse models for CIN. Figure 1 shows a schematic overview of a large number of genes that have been targeted for this purpose. One of the first models specifically designed to study the in vivo consequences of CIN is the Mad2 knockout mouse, targeting the spindle assembly checkpoint (SAC) (Dobles et al. 2000). The SAC prevents missegregation of chromosomes by inhibiting metaphase to anaphase progression until all chromosomes are properly attached to kinetochores in a bi-oriented fashion. Defects of the SAC therefore result in flawed chromosome segregation, which makes the SAC an attractive target to model CIN in vivo. A second means to induce CIN in vivo is by interfering with kinetochore integrity, a protein structure that connects the centromeric DNA to the mitotic spindle. This has been done by removing structural components of the kinetochore (e.g., CenpB, CenpC) or alternatively, by stabilizing kinetochore-microtubule attachments through e.g., overexpressing Mad2 or Hec1 (Díaz-Rodríguez et al. 2008; Kabeche and Compton 2012). Centrosomes are the microtubule-organizing centres in the cell from which the mitotic spindle emanates (Ganem et al. 2007; Gordon et al. 2012). Abnormal centrosome numbers can either result in multipolar divisions or, when supranumerary centrosomes cluster, predispose for lagging chromosomes in mitosis (Ganem et al. 2009). Therefore, a third way to provoke CIN in vivo is by inducing centrosome amplification, e.g., through overexpression of Plk4 (Ko et al. 2005; Marthiens et al. 2013a). A fourth approach to induce CIN in vivo is by disrupting the cohesion complex, a ring like structure that holds the sister chromatids together during interphase. Cohesion defects have been modelled by abrogating components of the cohesion complex (e.g., SA1), but also by deregulating upstream players such as pRb (Coschi et al. 2010; Manning et al. 2010; Van Harn et al. 2010). Similarly, various other genes have been knocked out in the mouse which indirectly affect chromosome segregation.



**Fig. 1** Schematic overview of various genes targeted to provoke CIN in vivo

### 3 In Vivo Consequences of CIN

In the last two decades, a large number of mouse models for chromosome instability have been engineered. Hereunder, we summarize the findings from these models asking the following questions:

1. Is CIN a bona fide instigator of cancer?
2. Which genes collaborate with CIN in vivo converting aneuploid cells into aneuploid cancer cells?
3. What are other consequences of CIN in vivo?

## 4 Can CIN Initiate Cancer?

CIN has detrimental consequences for cells grown in vitro (Kops et al. 2004; Williams et al. 2008; Torres et al. 2008), yet, two out of three human tumours are aneuploid (Weaver and Cleveland 2006; Duijf et al. 2013). This raises the question whether CIN is an initiating factor in cancer, a facilitator or merely a side effect of tumorigenesis. In the vast majority of all models (see Fig. 1), full inactivation of the targeted genes resulted in early embryonic lethality. Although the time of embryonic death varied between genotypes (Table 1), embryos were typically lost before embryonic day 10, which presumably was the result of aneuploidy in the inner cell mass of the developing embryos (Dobles et al. 2000; Weaver and Cleveland 2006; Fojer et al. 2008; Holland and Cleveland 2009; Schwartzman et al. 2010). To circumvent embryonic lethality, phenotypes of heterozygous mice were monitored, or in some cases, conditional alleles were engineered. Even though tumour phenotypes have been reported for many of these models (Table 1) tumour incidence is relatively low, with in most cases fewer than 50 % of the mice developing cancer. Moreover, tumours only arise late in the life of the mice, with latencies typically ranging from 12 to 24 months (Table 1). The most frequent pathologies observed include lymphoma, lung and liver tumours. Furthermore, not all models develop spontaneous tumours, for instance in case of the Bub family members [Bub1, Bub3, Rae1 (Kalitsis 2000; Babu et al. 2003; Wang et al. 2004; Baker et al. 2006a; Jeganathan et al. 2007; Baker et al. 2009)]. There is no clear correlation between the severity of the tumour phenotypes and the mechanism that drove CIN in the mice (i.e. SAC mutation, cohesion defects, centrosome abnormalities etc.). Expression levels of the CIN-provoking genes on the other hand appear to be a better predictor of tumour incidence: phenotypes were most severe in cases where CIN-driving proteins were overexpressed to high levels [e.g. Mad2, Cyclin B1, Cyclin B2, Hec1, Plk4 (Ko et al. 2005; Sotillo et al. 2007; Baker et al. 2008; Diaz-Rodríguez et al. 2008)] possibly because the relative effect on protein expression (several folds overexpression) was more dramatic than in heterozygous mice, where protein levels were typically reduced ~50 %. However, as tumour latency is high in these models as well, additional hits must be required for aneuploid cells to become malignant.

---

## 5 Does CIN Predispose to Cancer?

Exposure to carcinogens is a powerful tool to assess tumour predisposition in vivo. Given the relative weak tumour phenotypes of CIN mice, various CIN models were exposed to carcinogens (Table 1) to assess whether CIN is a powerful collaborator in transforming cells. Indeed, carcinogens aggravated the tumour phenotypes of some of the CIN mice, more than their control counterparts. For instance, when Mad1 heterozygous mice were treated with Vincristine (a microtubule-depolymerizing agent), 40 % of the mice developed mostly lung tumours, while no tumours were detected in control-treated mice (Iwanaga et al. 2007). Likewise, carcinogens

**Table 1** List of various mouse models engineered to provoke CIN in vivo, with phenotypes and observed aneuploidy levels in vivo and in vitro where quantified

Group	Gene	-/-	±		Cancer predisposed (chemical or genetic collaboration)	Aneuploidy in tissues	Aneuploidy in MEFs	Implicated in human cancer (Schvartzman et al. 2010)	References
Spindle assembly checkpoint	AuroraB	EL	>60 %; 24 mo		Tumour suppression upon DMBA + TPA-induced (not sig.)	ND	ND		Fernández-Miranda et al. (2011)
	Bub1	EL (E6.5)	VNODD		DMBA-induced-57 %, p53 <sup>+/+</sup> ; 16.6 mo	ND	ND		Jeganathan et al. (2007), Baker et al. (2009)
	Bub1 hypomorph	n/a	50 %; 12 mo		78 %, p53 <sup>+/+</sup> ; 12 mo	ND	15 % (seg. defects)		Jeganathan et al. (2007), Baker et al. (2009)
	Bub3	EL (E6.5)	VNODD		DMBA-induced	10 % (splenocytes)	20 %		Kalitsis (2000), Babu et al. (2003), Kalitsis et al. (2005), Baker et al. (2006b)
	Bub3; Rae1	ND	VNODD		DMBA-induced	40 % (splenocytes)	40 %		Babu et al. (2003), Baker et al. (2006b)
	BubR1	EL (E6.5)	VNODD		DMBA-induced	Polyploidy in megakaryocytes	15 %	Yes	Wang et al. (2004), Baker et al. (2004)
	BubR1 hypomorph	n/a	Premature ageing		DMBA- and azoxymethane-induced	30 % (splenocytes)	35 %	Yes (MVA)	Baker et al. (2004)
	BubR1 overexpression	n/a	Delayed ageing		DMBA-induced, but decreased susceptibility than WT	1 % (splenocytes)	9 % (WT comparable)		Baker et al. (2013a)
	Ccnb1 (Cyclin B1) overexpression	n/a	>75 %; (lung, lymphoma, liver, lipoma)		~80 %, APC+/min; 40 % (WT comparable; skin), DMBA-treatment	hi 20 %, lo 12 % (splenocytes)	31 % (ctrl. 15 %)		Nam and van Deursen (2014)

(continued)

Table 1 (continued)

Group	Gene	—/+	±	Cancer predisposed (chemical or genetic collaboration)	Aneuploidy in tissues	Aneuploidy in MEFs	Implicated in human cancer (Schvartzman et al. 2010)	References
	Cdc20 AAA mutant (does not bind to Mad2)	EL (E12.5)	50 %; 24 mo	ND	35 % (Cdc20 <sup>AAA/+</sup> , splenocytes)	28 % (Cdc20 <sup>AAA/+</sup> and 52 % of		Li et al. (2009)
	Cdh1	EL (E10.5)	17 % females – (mammary); mild brain abnormalities and altered behaviour	Tumour suppression upon TPA/DMBA treatment	ND	Increased (not quantified)		García-Higuera et al. (2008)
	CENPE	EL (<E7.5)	20 % (lung, spleen); 19–21 mo	Tumour suppression upon DMBA treatment or p19 <sup>Arf</sup> loss	40 % (splenocytes)	20 % (up to 70 % at high passage)		Weaver et al. (2003, 2007)
	Mad1	EL	20 % (lung); 18–20 mo	Vinorelbine-induced	ND	10 %		Iwanaga et al. (2007)
	Mad2	EL	30 % (lung); 18 mo	ND	ND	55 %		Dobles et al. (2000), Michel et al. (2001)
	Mad2 overexpression	n/a	50 % (lymphomas, lung and liver); 20 mo	DMBA-induced	Aneuploid tumours (not quantified)	50 %	Yes	Sotillo et al. (2007)
	Mps1 (T-cell restricted)	V/NOD	~ 50 % (lymphoma) 17 mo	100 % p53 <sup>+/+</sup> ; 5 mo	>90 % of cells aneuploid	ND		Foijer et al. (2014)
	Rae1	EL (E6.5)	No spont. tumorigenesis	DMBA-induced	10 % (splenocytes)	20 %		Babu et al. (2003), Baker et al. (2006b)
	UbcH10 overexpression	n/a	Expression level dependent: 40–80 % (lymphoma, lung adenoma, lipoma and liver and skin)	Yes, but not significantly different compared to wild type	4–19 % hi-lo, 5 mo (splenocytes); 52–64 % (lymphoma)	28–33 % (WT 13 %)	Yes	van Ree et al. (2010)

(continued)

Table 1 (continued)

Group	Gene	-/-	±	Cancer predisposed (chemical or genetic collaboration)	Aneuploidy in tissues	Aneuploidy in MEFs	Implicated in human cancer (Schvartzman et al. 2010)	References
Kinetochores	CENPA	EL (E6.5)	VNODD	ND	Chromosome missegregation in E6.5 CENPA <sup>-/-</sup> embryos	n/a		Howman et al. (2000)
	CENPB	VNODD	VNODD	ND	ND	ND		Hudson et al. (1998), Perez-Castro et al. (1998), Kapoor et al. (1998)
	CENPC	EL (E3.5)	VNODD	ND	Aberrant mitosis and micronuclei in early embryos	n/a		Kalitsis et al. (1998)
	Hec1 overexpression	n/a	13 % (lung), 26 % (liver); 67 wk, 60 wk	ND	ND	25 %	Yes	Diaz-Rodriguez et al. (2008)
Cohesion	Esp11 (separase)	EL (E6.5)	Eps11 <sup>+H</sup> ; VNODD	86 % (lymphomas), p53 <sup>-/-</sup> ; 4 mo–50 % (carcinoma), p53 <sup>+/-</sup>	57 % (splenocytes); 84 % (bone marrow)	ND	Yes	Mukherjee et al. (2011)
	Esp11 overexpression (mammary restricted)	n/a	80 % (mammary), 11 mo	100 % (mammary), p53 <sup>+/-</sup> ; 14 mo	>80 % (mammary tumours)	ND		Mukherjee et al. (2013)
	Slag1 (exon 3 and 4, encoding SA1-cohesin subunit)	EL (between E12.5 to E18.5)	40–50 % (haematoma, lung, fibrosarcoma, liver, vascular, pancreas); 24 mo	Resistance to 3MC and DEN induced fibrosarcomas and liver tumours	40 % (fetal liver)	>70 %		Remeseiro et al. (2012)
	Ptg (securin)	Reduced testis, spleen and thymus weight.	n/a	Tumour protective, pRb <sup>+/-</sup>	ND	15 % (WT 1 %)		Wang et al. (2001), Chesnokova et al. (2005)

(continued)



Table 1 (continued)

Group	Gene	-/-	±	Cancer predisposed (chemical or genetic collaboration)	Aneuploidy in tissues	Aneuploidy in MEFs	Implicated in human cancer (Schvartzman et al. 2010)	References
Chromosome passengers	Ptg (securin) overexpression	n/a	Enlarged pituitary; altered nuclear morphology	>80 % (pituitary), pRb <sup>-/-</sup> ; 10 mo	ND	ND		Abbud et al. (2005), Donangelo et al. (2006)
	APC/MIN	EL (<E8.5)	Intestinal tumours; 3 mo	ND	Aneuploidy and abnormal mitosis in crypt cells	Increased, not quantified		Su et al. (1992), Oshima et al. (1995), Rao et al. (2005), Caldwell et al. (2007)
	Incnp	EL (3.5–8.5)	VNODD	ND	Abnormal nuclear morphology hyperdiploid content in E3.5 embryos	n/a		Uren et al. (2000)
	Survivin	EL (6.5)	VNODD	ND	Giant nuclei in early embryos	n/a		Uren et al. (2000)
Centrosome	Aurora A overexpression (mammary restricted)	n/a	Increased p16 expression	45 %, p53 <sup>-/-</sup> (mammary gland); 4.5 mo	ND	13.6 %		Zhang et al. (2004, 2008)
	Plk1	EL (E10.5)	27.5 % (lymphoma, lung); 12.5–17.5 mo	100 % (lymphoma, lung), p53 <sup>-/-</sup>	12 % (splenocytes)	ND		Lu et al. (2008)
	Plk4 overexpression (CNS restricted)	n/a	Microcephaly, 100 % post-natal lethality; <1 wk	100 % lethality, p53 <sup>-/-</sup> ; 5 mo	31.7 % centrosome amplification (neural stem cells); >60 % aneuploidy of chr. 18 in p53 <sup>-/-</sup>	ND		Marthiens et al. (2013b)

(continued)

Table 1 (continued)

Group	Gene	-/-	±	Cancer predisposed (chemical or genetic collaboration)	Aneuploidy in tissues	Aneuploidy in MEFs	Implicated in human cancer (Schvartzman et al. 2010)	References
Otherwise involved in mitosis	Usp44	VNODD	Usp44 <sup>+/-</sup> 20 %, Usp44 <sup>-/-</sup> 50 %; 15 mo (lung, liver, lymphoma, sarcoma)	n/a	8 %, 5 mo; 16 %, 15 mo (splenocytes)	18 % (WT 13 %)	Yes	Zhang et al. (2012)
	Ccnb2 (Cyclin B2) overexpression	n/a	>70 % (lung, lymphoma, liver, lipoma); 14 mo	>80 %, APC <sup>+/-min</sup> ; >80 % (lung), DMBA-treatment	18 % (splenocytes)	36 % (ctrl. 16 %)		Nam and van Deursen (2014)
	Chfr	VNODD	Chfr <sup>-/-</sup> 50 %; 20 mo	DMBA-induced	ND	25 %		Yu et al. (2005)
	Mcm4 Chaos3	Chaos <sup>3/-</sup> EL (E14.5)	Mcm4Chaos <sup>3/+</sup> (mammary); 12 mo	ND	ND	ND		Shima et al. (2007)
	Tpx2	EL (E8.5)	53 % (lymphoma, lung)	no	18.3 %, 16 wk; 27 %, 90 wk (splenocytes) 48.9 %, 90 wk (lymphomas)			Aguirre-Portolés et al. (2012)

Genes that have been used to generate CIN mouse models  
EL embryonic lethal; VNODD viable, no overt developmental defects; ND not determined; n/a not applicable

(NMBA or DMBA) accelerated tumorigenesis in *Lzts1*-deficient and *Chfr*-deficient mice (Yu et al. 2005; Vecchione et al. 2007). Furthermore, even in CIN mice without a tumour phenotype (e.g., *Bub1*<sup>+/-</sup>, *Bub3*<sup>+/-</sup>, *Rae1*<sup>+/-</sup> and *Bub3*<sup>+/-</sup> *Rae1*<sup>+/-</sup>), DMBA treatment had a stronger tumour promoting effect than on wild type mice (Baker et al. 2006b; Jeganathan et al. 2007). As carcinogens reduce tumour latency and increase tumour incidence in a CIN background, also these experiments indicate that additional mutations are required for a CIN cell to transform into a malignant cell.

---

## 6 Which Genes Collaborate with CIN in Cancer?

To test which genetic alterations collaborate with CIN in tumorigenesis, various CIN models were crossed into cancer-predisposed backgrounds. For instance, when CIN was combined with p53 heterozygosity, [*Bub1*, *Esp1*, *Mps1* (Baker et al. 2009; Mukherjee et al. 2011; Baker et al. 2013b)] tumour incidence dramatically increased while tumour latencies decreased. In all reported cases, tumours had lost the remaining p53 wild type allele, indicating that full p53 loss and CIN synergize in tumorigenesis (Baker et al. 2009; Foijer et al. 2014). However, as CIN further increased tumour incidence of p53<sup>null</sup> mice, CIN must have facilitated cancer formation through additional genomic alterations as well. Furthermore, CIN provoked by *Bub1* hypomorphic alleles or Cyclin B1 overexpression accelerates tumours in a *Apc*<sup>min</sup> background (Baker et al. 2008, 2009). However, in other tumour predisposed backgrounds (e.g., pRb or *Pten* heterozygosity) CIN has no effect on tumour incidence (Baker et al. 2009).

---

## 7 CIN as a Tumour Suppressor

In some cases CIN can also act in a tumour suppressive manner. For instance, CIN driven by *SA1* heterozygosity delays 3-methyl-colanthrene (3-MC)-induced fibrosarcoma and diethyl-nitrosamine (DEN)-induced liver tumours (Remeseiro et al. 2012). Similarly, even though *Cdh1*<sup>+/-</sup> mice and *CenPE*<sup>+/-</sup> mice are more susceptible to spontaneous tumours, they are more resistant to carcinogenic insults than their wild type counterparts (Weaver et al. 2007; García-Higuera et al. 2008). Furthermore, CIN can also delay tumorigenesis in some genetically predisposed models, for instance by delaying p19<sup>Arf</sup> or *Pten* loss-driven tumours (Weaver et al. 2007; Baker et al. 2009). Why then is CIN tumour promoting in one setting, but tumour suppressive in another? The answer might lie in the levels of CIN. CIN is quite toxic and provokes an ‘aneuploidy stress’ response in untransformed cells (Kops et al. 2004; Torres et al. 2007; Williams et al. 2008; Foijer et al. 2013). However, aneuploid cancer cells also exhibit this stress response (Dürbaum et al. 2014; Foijer et al. 2014), suggesting that aneuploid cancer cells still suffer from the disadvantageous effects of CIN. Therefore, the levels of CIN occurring in pre-malignant cells could be a determining factor for the outcome. The fact that p19<sup>Arf</sup> loss provokes aneuploidy itself fits with this hypothesis, as *CenPE* heterozygosity would

exacerbate CIN to a level that is toxic for cancer cells (Silk et al. 2013). However, further experiments are required to determine at what level CIN is beneficial for cancer cells and at what level the balance is tipped.

---

## 8 What Other Phenotypes Are Provoked by CIN?

There is increasing evidence that aneuploidy also occurs in untransformed tissues, with liver being the most well-known example. Up to half of both human and murine hepatocytes are aneuploid (Duncan et al. 2012a, b), but it is unclear why hepatocytes evolved to become aneuploid. One suggestion is that particular karyotypes are selected for during hepatotoxic insults, making the hepatocytes more resistant to injury (Duncan et al. 2012b). Other studies quantified over 30 % of normal human neuroblasts to be aneuploid (Rehen et al. 2001, 2005), which has been suggested to contribute to the plasticity of neurons (Kingsbury et al. 2005). However, when provoked in a random fashion, CIN appears to mostly have disadvantageous effects on brain functioning, as mice heterozygous for *Cdh1* exhibit defects in neuromuscular coordination and learning (García-Higuera et al. 2008). The interfollicular epidermal cells in mouse skin on the other hand appear to cope surprisingly well with CIN as they tolerate full abrogation of the SAC provoked by *Mad2* loss, which results in dramatic aneuploidy (Fojer et al. 2013). The hair follicle stem cells that reside in the same compartment do not cope at all and disappear, resulting in mice with functional skin, but without hair (Fojer et al. 2013). Together these data clearly indicate that CIN is tolerated by some cell lineages, but not others, underscoring the importance of in vivo modelling.

---

## 9 Linking Ageing and CIN In Vivo

Ageing is the time-dependent functional decline in the fitness of cells, organs and organisms. A common hallmark of ageing is genomic instability, as exemplified by genetic alterations in old blood cells (Forsberg et al. 2012; López-Otín et al. 2013). Some of the CIN mouse models also suggest a role for aneuploidy in ageing. For instance, *BubR1* hypomorphic mice are not only prone to severe aneuploidization, but also display progeroid pathologies. Similar to *BubR1*, combined *Bub3/Rae1* haploinsufficiency also results in a premature ageing phenotype, albeit less severe than the *BubR1* hypomorphic mice (Baker et al. 2006b), MEFs isolated from *BubR1* hypomorphic mice express various ageing-associated markers such as p53, p21, p19<sup>Arf</sup> and p16<sup>Ink4a</sup>. Interestingly, when p16<sup>Ink4a</sup> positive cells are killed in vivo using a p16<sup>Ink4a</sup>-promotor regulated suicide construct, ageing pathologies induced by a reduction of *BubR1* protein levels are dramatically delayed (Baker et al. 2011). The pathologies observed in *BubR1* hypomorphic mice mimic those of patients with multi-variegated aneuploidy (MVA), a disease that frequently coincides with mutations in *BUB1B*, the gene encoding BUBR1 (Hanks et al. 2004,

2006; Matsuura et al. 2006). Furthermore, BubR1 expression levels decline with age providing further evidence for a role of BubR1 in ageing (Baker et al. 2011) in mice. Even more striking, when BubR1 is overexpressed, a dose-dependent delay in the onset of ageing is observed, as well as protection against developing chemically-induced tumours (Baker et al. 2013a). As discussed above, in most tested cases overexpression of CIN-controlling proteins increases CIN and predisposes for cancer (Sotillo et al. 2007; Diaz-Rodríguez et al. 2008; Fernández-Miranda et al. 2011). Apparently, BubR1 is the exception that forms the rule, but future work should reveal whether BubR1 has a unique role in the SAC or whether it has additional roles that can explain the beneficial effects of an overdose of BubR1.

---

## 10 What Have We Learnt from Modelling CIN in the Mouse so Far?

As most tumours are aneuploid to some extent, CIN makes an attractive target for therapy. For this, understanding how CIN is signalled is crucial. A large number of mouse models have been engineered over the last 15 years specifically for this purpose, with a wide variety of phenotypes summarized in Table 1. Even though many of the targeted genes will have other roles than safeguarding faithful chromosome segregation, some common conclusions can be drawn from the cumulative data. The first important conclusion is that CIN alone is not sufficient for efficient tumorigenesis and that CIN alone mostly has disadvantageous effects on cell proliferation. This has important implications for therapy targeting aneuploid cancer, as discussed below. A second conclusion is that CIN facilitates tumorigenesis efficiently in some tumour-predisposed backgrounds, chemical or genetic. However, when CIN is aggravated and becomes too severe, it can actually suppress tumour formation in the mouse, which can also be exploited in cancer therapy. A third and perhaps the most important conclusion is that several unaddressed questions remain before we can develop therapeutic strategies targeting aneuploid cell progeny, some of which are discussed below. Although all models discussed here were designed to study the consequences of CIN *in vivo*, the majority mimic a situation that is not typically found in human cancers, as loss of genes that regulate chromosome segregations are rarely lost in human cancer (Schvartzman et al. 2010; Foijer 2012). Even though those models mimic chromosome missegregation and its consequences, overexpression of CIN-modulating genes is more common [e.g., Mad2 overexpression, which is seen in many tumours (Hernando et al. 2004; Sotillo et al. 2007)]. Possibly, mimicking the CIN-provoking mutations that are found in human cancers would result in a physiologically more relevant CIN level, thus adding to our understanding of CIN and its role in tumorigenesis. A lot can be learned about affected pathways from *in vitro* studies as well. For instance, Donnelly and colleagues have shown that increased HSF1 activity can play a facilitating

role in coping with aneuploidy-induced proteotoxic stress by regulating the gene expression of various heat shock proteins (Donnelly et al. 2014)

---

## **11 Questions that Need to Be Addressed**

### **11.1 Which Mutations Make an Aneuploid Cell an Aneuploid Cancer Cell?**

Some tumour suppressor genes, (e.g., p53) were found to accelerate the malignant transformation of aneuploid cells, but the mechanism behind this collaboration remains unclear. As CIN alone is a poor initiator of cancer, pathways that convert aneuploid cells in aneuploid cancer cells make up important therapeutic targets. So far, CIN-collaborating genes were picked in an ‘educated guess’ approach. However, to identify in an unbiased fashion the pathways that convert CIN cells into CIN cancer cells, (in vivo) genetic screens are required.

### **11.2 At What Rate Is CIN Tumorigenic and at What Levels Tumour Suppressive?**

The effects of CIN across the various mouse models are diverse, but it is unclear why. It is inevitable that the levels of CIN are different among the various CIN models, but there is no clear correlation between the levels of aneuploidy and the resulting phenotype based on the available data. However, as the level of CIN might determine whether tumours are promoted or are suppressed (Silk et al. 2013), high resolution quantification of CIN will be crucial when targeted in therapy. Furthermore, even though aneuploidy is a hallmark of cancer, the actual rates of chromosome missegregation (i.e., the CIN rates) in human cancer are unknown. To quantify these, primary (tumour) cells need to be fully karyotyped at the single cell level at various stages. So far, most studies have relied on metaphase-spread based (spectral) karyotyping using dividing cell populations, such as primary MEFs or tumour cell lines. However, this technique cannot be applied to most primary tumour cells as they do not divide frequently (Mitchison 2012; McGranahan et al. 2012). A new, but costly approach to quantify karyotypes of single cells is next-generation sequencing (NGS) (Knouse et al. 2014; Bakker et al. 2015). However, to quantify aneuploidy, full coverage (or even multiple coverage) per cell is not a requirement. 1–2 % coverage per cell will be sufficient to quantify chromosome numbers for an individual cell, allowing sequencing libraries of many cells to be pooled in each sequencing lane. Single cell karyotyping will allow us to faithfully measure in vivo missegregation rates (i.e. CIN) by assessing subtle karyotype differences between cells within one tumour (karyotype heterogeneity) (Bakker et al. 2015). Such technology will allow us to determine at which rate CIN is tumorigenic or tumour suppressive in mouse models and what the CIN rates are in human primary tumours.

### 11.3 What Determines the Tissue Specific Response to CIN?

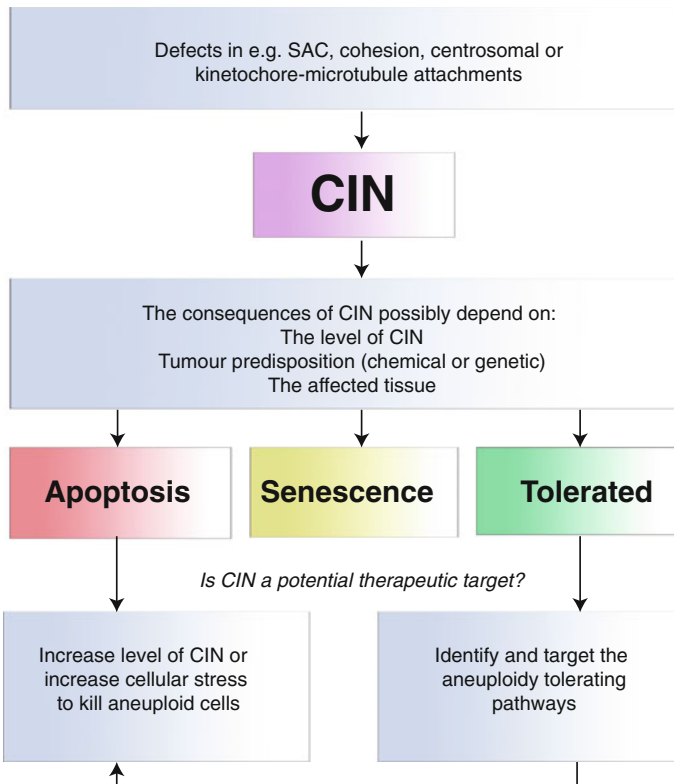
There is a marked difference as to how cell lineages respond to CIN. For instance, CIN is highly toxic to embryonic stem cells (Burds et al. 2005), but quite well tolerated by interfollicular epidermal cells (Fojer et al. 2013), hepatocytes and possibly neurons (Rehen et al. 2001, 2005; Kingsbury et al. 2005; Duncan et al. 2012a). As of yet, it remains unclear what determines this differential response. Possibly, some cell lineages such as stem cells, induce a stronger stress response upon aneuploidy, resulting in apoptosis or differentiation. Alternatively, aneuploidy-tolerating cells spend more time in pro-metaphase and therefore have more time to correct improper kinetochore-microtubule attachments, thus reducing the missegregation rates and therefore reducing aneuploidy to tolerable levels. Indeed some cell types tolerate at least some aneuploidy including neurons and hepatocytes. However, further *in vivo* experiments are required to assess which molecular pathways make up the response to aneuploidy at the tissue level and how the differential wiring of these pathways in different cell lineages determines the fate of aneuploid cells.

### 11.4 What Are the Molecular Mechanisms that Explain the Link Between CIN and Ageing?

Some of the CIN mouse models exhibit a premature ageing phenotype, most clearly knockout models of Bub family proteins (BubR1, Bub3/Rae1) (Baker et al. 2004, 2006b). Conversely, BubR1 transgenic mice show increased lifespan, clearly implicating BubR1 with ageing (Baker et al. 2013a). This data, together with the observation that BubR1 expression decreases with ageing in wild type animals, (Baker et al. 2004, 2006b), suggest that CIN may play a role in natural ageing. Why were phenotypes only described for Bub protein members? Possibly, (subtle) signs of premature ageing were overlooked in other CIN models, as these models were developed specifically to study the relationship between CIN and cancer and not ageing, (Ricke and van Deursen 2013). Indeed, a more detailed analysis of transcriptomes of *Mad2*<sup>null</sup> epidermal cells suggests an ageing-like response in murine skin following SAC abrogation (Fojer et al. 2013), suggesting that CIN indeed provokes a premature ageing response in untransformed tissue. However, more detailed and high resolution mapping of CIN in ageing human tissues is required to confirm physiological relevance for a potential link between CIN and ageing. When this link is confirmed, the underlying molecular mechanisms that link CIN and ageing should be elucidated, employing exciting and possibly new, more human relevant CIN mouse models.

## 11.5 What Is the Potential of CIN-Targeting Therapy?

Aneuploidy is a hallmark of cancer and selectively killing aneuploid cells would therefore be a powerful means to treat cancer. The various mouse models for CIN have revealed that there are three possible outcomes for aneuploid cell progeny depending on the tissue affected: (1) cell death (e.g., in case of hair follicle stem cells), (2) cellular senescence (evidenced by premature ageing and upregulation of the senescence marker p16<sup>Ink4a</sup>) and (3) tolerance of aneuploidy (Fig. 2). The latter outcome is the most dangerous, as proliferating aneuploid cells can further evolve into aneuploid cancer cells. Therefore, to target aneuploid cancer, those cells that tolerate aneuploidy will need to be forced to either commit suicide or senesce. There are multiple ways as to how such therapy could work, ranging from very broad spectrum to highly ‘personalized’ therapies. As discussed above, too much CIN is detrimental to cells (Silk et al. 2013). Therefore, further increasing CIN in aneuploid tumours could be a broad-spectrum way to target aneuploid cancer cells. Indeed, mild CIN renders cells more sensitive to therapeutics that exacerbate CIN such as low doses taxol (Janssen et al. 2009). However, the inherent risk to this therapy is



**Fig. 2** Flowchart summarizing the in vivo consequences of CIN and therapeutic promise



that untransformed (non-CIN) cells will also be exposed to CIN and might convert into a new CIN tumour over time. A second approach of targeting CIN cells is by modulating the pathways that regulate cell fate following aneuploidization. In this approach, the pathways that result in cell death of (embryonic) stem cells following CIN are artificially activated in aneuploid cancer cells, resulting in cancer cell death. However, before feasibility of such therapy can be assessed, CIN-responsive pathways need to be mapped first. Instead of targeting aneuploidy-signalling pathways, therapy can also target the downstream consequences of CIN. For instance, one common response to aneuploidy is a deregulation of cellular metabolism, which affects untransformed cells as well as cancer cells (Williams et al. 2008; Torres et al. 2008; Foijer et al. 2014). The first proof of principle evidence for such therapy is just emerging. Recent studies are showing that energy stress inducer AICAR and the Hsp190 inhibitor 17-AAG selectively can kill aneuploid (cancer) cells by enhancing aneuploidy-induced stress (Tang et al. 2011; Ly et al. 2013; García Martínez et al. 2014). The next step to this will be to test whether this is also effective in vivo. A fourth ‘personalised medicine’ approach to tackle aneuploid cancer is by targeting the mutation that is driving CIN. One candidate for such therapy is Hec1, as it is frequently overexpressed in a variety of cancers. Indeed, inhibition of the Hec1/Nek2 pathway results in reduced tumour growth in a xenograft mouse model (Wu et al. 2008), providing proof of principle evidence for this approach. Similarly, gene products that collaborate with CIN in transformation can be targeted using molecular therapy. For the latter, we first need to identify candidate targets, for instance in in vivo genetic screens. However, for molecular therapy full sequencing of the tumour is a requirement. However, as sequencing costs are rapidly decreasing and the number of specific pathway inhibitors are rapidly increasing, this approach might become feasible within the near future.

**Acknowledgements** We thank Georges Janssens for critically reading this manuscript and fruitful discussion. This work was supported by Stichting Kinder Oncologie funding and Dutch Cancer Society grant RUG 2012-5549.

---

## References

- Abbud RA, Takumi I, Barker EM et al (2005) Early multipotential pituitary focal hyperplasia in the alpha-subunit of glycoprotein hormone-driven pituitary tumor-transforming gene transgenic mice. *Mol Endocrinol* 19:1383–1391. doi:[10.1210/me.2004-0403](https://doi.org/10.1210/me.2004-0403)
- Aguirre-Portolés C, Bird AW, Hyman A, et al (2012) Tpx2 controls spindle integrity, genome stability, and tumor development. *Cancer Res* 72:1518–28. doi: [10.1158/0008-5472.CAN-11-1971](https://doi.org/10.1158/0008-5472.CAN-11-1971)
- Babu JR, Jeganathan KB, Baker DJ et al (2003) Rae1 is an essential mitotic checkpoint regulator that cooperates with Bub3 to prevent chromosome missegregation. *J Cell Biol* 160:341–353. doi:[10.1083/jcb.200211048](https://doi.org/10.1083/jcb.200211048)
- Baker DJ, Jeganathan KB, Cameron JD et al (2004) BubR1 insufficiency causes early onset of aging-associated phenotypes and infertility in mice. *Nat Genet* 36:744–749. doi:[10.1038/ng1382](https://doi.org/10.1038/ng1382)

- Baker DJ, Jeganathan KB, Malureanu L et al (2006) Early aging-associated phenotypes in Bub3/Rae1 haploinsufficient mice. *J Cell Biol* 172:529–540. doi:[10.1083/jcb.200507081](https://doi.org/10.1083/jcb.200507081)
- Baker DJ, Jin F, van Deursen JM (2008) The yin and yang of the Cdkn2a locus in senescence and aging. *Cell Cycle* 7:2795–2802
- Baker DJ, Jin F, Jeganathan KB, van Deursen JM (2009) Whole chromosome instability caused by Bub1 insufficiency drives tumorigenesis through tumor suppressor gene loss of heterozygosity. *Cancer Cell* 16:475–486. doi:[10.1016/j.ccr.2009.10.023](https://doi.org/10.1016/j.ccr.2009.10.023)
- Baker DJ, Wijshake T, Tchkonian T et al (2011) Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature* 479:232–236. doi:[10.1038/nature10600](https://doi.org/10.1038/nature10600)
- Baker DJ, Dawlaty MM, Wijshake T et al (2013a) Increased expression of BubR1 protects against aneuploidy and cancer and extends healthy lifespan. *Nat Cell Biol* 15:96–102. doi:[10.1038/ncb2643](https://doi.org/10.1038/ncb2643)
- Baker DJ, Weaver RL, van Deursen JM (2013b) p21 both attenuates and drives senescence and aging in BubR1 progeroid mice. *Cell Rep* 3:1164–1174. doi:[10.1016/j.celrep.2013.03.028](https://doi.org/10.1016/j.celrep.2013.03.028)
- Bakker B, van den Bos H, Lansdorp PM, Foijer F (2015) How to count chromosomes in a cell: An overview of current and novel technologies. *BioEssays* n/a–n/a. doi: [10.1002/bies.201400218](https://doi.org/10.1002/bies.201400218)
- Bignold LP, Coghlan BLD, Jersmann HPA (2006) Hansemann, Boveri, chromosomes and the gametogenesis-related theories of tumours. *Cell Biol Int* 30:640–644. doi:[10.1016/j.cellbi.2006.04.002](https://doi.org/10.1016/j.cellbi.2006.04.002)
- Boveri T (2008) Concerning the origin of malignant tumours by Theodor Boveri. Translated and annotated by Henry Harris. *J Cell Sci* 121(Suppl):1–84. doi: [10.1242/jcs.025742](https://doi.org/10.1242/jcs.025742)
- Boveri T, Manchester KL (1995) Theodor Boveri—the origin of malignant tumours. *Trends Cell Biol* 5:384–387
- Burds AA, Lutum AS, Sorger PK (2005) Generating chromosome instability through the simultaneous deletion of Mad2 and p53. *Proc Natl Acad Sci USA* 102:11296–11301. doi:[10.1073/pnas.0505053102](https://doi.org/10.1073/pnas.0505053102)
- Caldwell CM, Green RA, Kaplan KB (2007) APC mutations lead to cytokinetic failures in vitro and tetraploid genotypes in Min mice. *J Cell Biol* 178:1109–1120. doi:[10.1083/jcb.200703186](https://doi.org/10.1083/jcb.200703186)
- Chesnokova V, Kovacs K, Castro A-V et al (2005) Pituitary hypoplasia in Pttg<sup>-/-</sup> mice is protective for Rb± pituitary tumorigenesis. *Mol Endocrinol* 19:2371–2379. doi:[10.1210/me.2005-0137](https://doi.org/10.1210/me.2005-0137)
- Coschi CH, Martens AL, Ritchie K et al (2010) Mitotic chromosome condensation mediated by the retinoblastoma protein is tumor-suppressive. *Genes Dev* 24:1351–1363. doi:[10.1101/gad.1917610](https://doi.org/10.1101/gad.1917610)
- Díaz-Rodríguez E, Sotillo R, Schvartzman J-M, Benezra R (2008) Hec1 overexpression hyperactivates the mitotic checkpoint and induces tumor formation in vivo. *Proc Natl Acad Sci USA* 105:16719–16724. doi:[10.1073/pnas.0803504105](https://doi.org/10.1073/pnas.0803504105)
- Dobles M, Liberal V, Scott ML et al (2000) Chromosome missegregation and apoptosis in mice lacking the mitotic checkpoint protein Mad2. *Cell* 101:635–645
- Donangelo I, Gutman S, Horvath E et al (2006) Pituitary tumor transforming gene overexpression facilitates pituitary tumor development. *Endocrinology* 147:4781–4791. doi:[10.1210/en.2006-0544](https://doi.org/10.1210/en.2006-0544)
- Donnelly N, Passerini V, Dürbaum M, et al (2014) HSF 1 deficiency and impaired HSP 90 - dependent protein folding are hallmarks of aneuploid human cells. *EMBO J* 33:2374–2387. doi: [10.15252/embj.201488648](https://doi.org/10.15252/embj.201488648)
- Duijff PHG, Schultz N, Benezra R (2013) Cancer cells preferentially lose small chromosomes. *Int J Cancer* 132:2316–2326. doi:[10.1002/ijc.27924](https://doi.org/10.1002/ijc.27924)
- Duncan AW, Hanlon Newell AE, Smith L et al (2012a) Frequent aneuploidy among normal human hepatocytes. *Gastroenterology* 142:25–28. doi:[10.1053/j.gastro.2011.10.029](https://doi.org/10.1053/j.gastro.2011.10.029)
- Duncan AW, Newell AEH, Bi W et al (2012b) Aneuploidy as a mechanism for stress-induced liver adaptation. *J Clin Invest* 122:3307–3315. doi:[10.1172/JCI64026DS1](https://doi.org/10.1172/JCI64026DS1)
- Dürbaum M, Kuznetsova AY, Passerini V et al (2014) Unique features of the transcriptional response to model aneuploidy in human cells. *BMC Genom* 15:139

- Faggioli F, Wang T, Vijg J, Montagna C (2012) Chromosome-specific accumulation of aneuploidy in the aging mouse brain. *Hum Mol Genet* 1–8. doi: [10.1093/hmg/dds375](https://doi.org/10.1093/hmg/dds375)
- Fernández-Miranda G, Trakala M, Martín J et al (2011) Genetic disruption of aurora B uncovers an essential role for aurora C during early mammalian development. *Development* 138:2661–2672. doi: [10.1242/dev.066381](https://doi.org/10.1242/dev.066381)
- Foijer F (2012) Mouse models for chromosomal instability. In: Storchova Z (ed) *Aneuploidy Heal Dis Intech* 59–78
- Foijer F, Draviam VM, Sorger PK (2008) Studying chromosome instability in the mouse. *Biochim Biophys Acta* 1786:73–82. doi: [10.1016/j.bbcan.2008.07.004](https://doi.org/10.1016/j.bbcan.2008.07.004)
- Foijer F, Ditommaso T, Donati G et al (2013) Spindle checkpoint deficiency is tolerated by murine epidermal cells but not hair follicle stem cells. *Proc Natl Acad Sci USA*. doi: [10.1073/pnas.1217388110](https://doi.org/10.1073/pnas.1217388110)
- Foijer F, Xie SZ, Simon JE, et al (2014) Chromosome instability induced by Mps1 and p53 mutation generates aggressive lymphomas exhibiting aneuploidy-induced stress. *Proc Natl Acad Sci*. doi: [10.1073/pnas.1400892111](https://doi.org/10.1073/pnas.1400892111)
- Forsberg LA, Rasi C, Razzaghi HR et al (2012) Age-related somatic structural changes in the nuclear genome of human blood cells. *Am J Hum Genet* 90:217–228. doi: [10.1016/j.ajhg.2011.12.009](https://doi.org/10.1016/j.ajhg.2011.12.009)
- Ganem NJ, Storchova Z, Pellman D (2007) Tetraploidy, aneuploidy and cancer. *Curr Opin Genet Dev* 17:157–162. doi: [10.1016/j.gde.2007.02.011](https://doi.org/10.1016/j.gde.2007.02.011)
- Ganem NJ, Godinho SA, Pellman D (2009) A mechanism linking extra centrosomes to chromosomal instability. *Nature* 460:278–282. doi: [10.1038/nature08136](https://doi.org/10.1038/nature08136)
- García Martínez J, García-Inclán C, Suárez C, et al (2014) DNA aneuploidy-specific therapy for head and neck squamous cell carcinoma. *Head Neck* 1–5. doi: [10.1002/hed.23687](https://doi.org/10.1002/hed.23687)
- García-Higuera I, Manchado E, Dubus P et al (2008) Genomic stability and tumour suppression by the APC/C cofactor Cdh1. *Nat Cell Biol* 10:802–811. doi: [10.1038/ncb1742](https://doi.org/10.1038/ncb1742)
- Gordon DJ, Resio B, Pellman D (2012) Causes and consequences of aneuploidy in cancer. *Nat Rev Genet* 13:189–203. doi: [10.1038/nrg3123](https://doi.org/10.1038/nrg3123)
- Hanks S, Coleman K, Reid S et al (2004) Constitutional aneuploidy and cancer predisposition caused by biallelic mutations in BUB1B. *Nat Genet* 36:1159–1161. doi: [10.1038/ng1449](https://doi.org/10.1038/ng1449)
- Hanks S, Coleman K, Summersgill B et al (2006) Comparative genomic hybridization and BUB1B mutation analyses in childhood cancers associated with mosaic variegated aneuploidy syndrome. *Cancer Lett* 239:234–238. doi: [10.1016/j.canlet.2005.08.006](https://doi.org/10.1016/j.canlet.2005.08.006)
- Hardy PA, Zacharias H (2005) Reappraisal of the Hanseman-Boveri hypothesis on the origin of tumors. *Cell Biol Int* 29:983–92. doi: [10.1016/j.cellbi.2005.10.001](https://doi.org/10.1016/j.cellbi.2005.10.001)
- Hernando E, Nahlé Z, Juan G et al (2004) Rb inactivation promotes genomic instability by uncoupling cell cycle progression from mitotic control. *Nature* 430:797–802. doi: [10.1038/nature02820](https://doi.org/10.1038/nature02820)
- Holland AJ, Cleveland DW (2009) Boveri revisited: chromosomal instability, aneuploidy and tumorigenesis. *Nat Rev Mol Cell Biol* 10:478–487. doi: [10.1038/nrm2718](https://doi.org/10.1038/nrm2718)
- Howman EV, Fowler KJ, Newson AJ et al (2000) Early disruption of centromeric chromatin organization in centromere protein A (Cenpa) null mice. *Proc Natl Acad Sci U S A* 97:1148–1153
- Hudson DF, Fowler KJ, Earle E et al (1998) Centromere protein B null mice are mitotically and meiotically normal but have lower body and testis weights. *J Cell Biol* 141:309–319
- Iourov IY, Vorsanova SG, Liehr T, Yurov YB (2009) Aneuploidy in the normal, Alzheimer's disease and ataxia-telangiectasia brain: differential expression and pathological meaning. *Neurobiol Dis* 34:212–220. doi: [10.1016/j.nbd.2009.01.003](https://doi.org/10.1016/j.nbd.2009.01.003)
- Iwanaga Y, Chi Y-H, Miyazato A et al (2007) Heterozygous deletion of mitotic arrest-deficient protein 1 (MAD1) increases the incidence of tumors in mice. *Cancer Res* 67:160–166. doi: [10.1158/0008-5472.CAN-06-3326](https://doi.org/10.1158/0008-5472.CAN-06-3326)

- Janssen A, Kops GJPL, Medema RH (2009) Elevating the frequency of chromosome mis-segregation as a strategy to kill tumor cells. *Proc Natl Acad Sci U S A* 106:19108–19113. doi:[10.1073/pnas.0904343106](https://doi.org/10.1073/pnas.0904343106)
- Janssen A, van der Burg M, Suzhai K et al (2011) Chromosome segregation errors as a cause of DNA damage and structural chromosome aberrations. *Science* (80-) 333:1895–1898. doi:[10.1126/science.1210214](https://doi.org/10.1126/science.1210214)
- Jeganathan K, Malureanu L, Baker DJ et al (2007) Bub1 mediates cell death in response to chromosome missegregation and acts to suppress spontaneous tumorigenesis. *J Cell Biol* 179:255–267. doi:[10.1083/jcb.200706015](https://doi.org/10.1083/jcb.200706015)
- Kabeche L, Compton Da (2012) Checkpoint-independent stabilization of kinetochore-microtubule attachments by Mad2 in human cells. *Curr Biol* 22:638–644. doi:[10.1016/j.cub.2012.02.030](https://doi.org/10.1016/j.cub.2012.02.030)
- Kalitsis P (2000) Bub3 gene disruption in mice reveals essential mitotic spindle checkpoint function during early embryogenesis. *Genes Dev* 14:2277–2282. doi:[10.1101/gad.827500](https://doi.org/10.1101/gad.827500)
- Kalitsis P, Fowler KJ, Earle E et al (1998) Targeted disruption of mouse centromere protein C gene leads to mitotic disarray and early embryo death. *Proc Natl Acad Sci USA* 95:1136–1141
- Kalitsis P, Fowler KJ, Griffiths B et al (2005) Increased chromosome instability but not cancer predisposition in haploinsufficient Bub3 mice. *Genes Chromosom Cancer* 44:29–36. doi:[10.1002/gcc.20215](https://doi.org/10.1002/gcc.20215)
- Kapoor M, de Oca Montes, Luna R, Liu G et al (1998) The cenpB gene is not essential in mice. *Chromosoma* 107:570–576
- Kingsbury MA, Friedman B, McConnell MJ et al (2005) Aneuploid neurons are functionally active and integrated into brain circuitry. *Proc Natl Acad Sci USA* 102:6143–6147. doi:[10.1073/pnas.0408171102](https://doi.org/10.1073/pnas.0408171102)
- Knouse KA, Wu J, Whittaker CA, Amon A (2014) Single cell sequencing reveals low levels of aneuploidy across mammalian tissues. *Proc Natl Acad Sci* 111:13409–13414. doi:[10.1073/pnas.1415287111](https://doi.org/10.1073/pnas.1415287111)
- Ko MA, Rosario CO, Hudson JW et al (2005) Plk4 haploinsufficiency causes mitotic infidelity and carcinogenesis. *Nat Genet* 37:883–888. doi:[10.1038/ng1605](https://doi.org/10.1038/ng1605)
- Kops GJPL, Foltz DR, Cleveland DW (2004) Lethality to human cancer cells through massive chromosome loss by inhibition of the mitotic checkpoint. *Proc Natl Acad Sci USA* 101:8699–8704. doi:[10.1073/pnas.0401142101](https://doi.org/10.1073/pnas.0401142101)
- Lai F, Williams RS (1989) A prospective study of Alzheimer disease in Down syndrome. *Arch Neurol* 46:849–853
- Li M, Fang X, Wei Z et al (2009) Loss of spindle assembly checkpoint-mediated inhibition of Cdc20 promotes tumorigenesis in mice. *J Cell Biol* 185:983–994. doi:[10.1083/jcb.200904020](https://doi.org/10.1083/jcb.200904020)
- López-Otín C, Blasco MA, Partridge L et al (2013) The hallmarks of aging. *Cell* 153:1194–1217. doi:[10.1016/j.cell.2013.05.039](https://doi.org/10.1016/j.cell.2013.05.039)
- Lu L-Y, Wood JL, Minter-Dykhouse K et al (2008) Polo-like kinase 1 is essential for early embryonic development and tumor suppression. *Mol Cell Biol* 28:6870–6876. doi:[10.1128/MCB.00392-08](https://doi.org/10.1128/MCB.00392-08)
- Ly P, Kim SB, Wright WE, et al (2013) Aneuploid human colonic epithelial cells are sensitive to AICAR-induced growth inhibition through EGFR degradation. *Oncogene* 32:3139–3146. doi:[10.1158/1538-7445.AM2012-3863](https://doi.org/10.1158/1538-7445.AM2012-3863)
- Manning AL, Longworth MS, Dyson NJ (2010) Loss of pRB causes centromere dysfunction and chromosomal instability. *Genes Dev* 24:1364–1376. doi:[10.1101/gad.1917310](https://doi.org/10.1101/gad.1917310)
- Marthiens V, Rujano MA, Penner C et al (2013) Centrosome amplification causes microcephaly. *Nat Cell Biol* 15:731–740. doi:[10.1038/ncb2746](https://doi.org/10.1038/ncb2746)
- Matsuura S, Matsumoto Y, Morishima K, et al (2006) Monoallelic BUB1B mutations and defective mitotic-spindle checkpoint in seven families with premature chromatid separation (PCS) syndrome. 367:358–367. doi:[10.1002/ajmg.a](https://doi.org/10.1002/ajmg.a)
- McGranahan N, Burrell RA, Endesfelder D et al (2012) Cancer chromosomal instability: therapeutic and diagnostic challenges. *EMBO Rep* 13:528–538. doi:[10.1038/embor.2012.61](https://doi.org/10.1038/embor.2012.61)

- Michel LS, Liberal V, Chatterjee A, et al (2001) Premature anaphase and chromosome instability in mammalian cells. 355–359
- Mitchison TJ (2012) The proliferation rate paradox in antimitotic chemotherapy. *Mol Biol Cell* 23:1–6. doi:[10.1091/mbc.E10-04-0335](https://doi.org/10.1091/mbc.E10-04-0335)
- Mukherjee M, Ge G, Zhang N et al (2011) Separase loss of function cooperates with the loss of p53 in the initiation and progression of T- and B-cell lymphoma, leukemia and aneuploidy in mice. *PLoS ONE* 6:e22167. doi:[10.1371/journal.pone.0022167](https://doi.org/10.1371/journal.pone.0022167)
- Mukherjee M, Ge G, Zhang N, et al (2013) MMTV-Esp11 transgenic mice develop aneuploid, estrogen receptor alpha (ER $\alpha$ )-positive mammary adenocarcinomas. *Oncogene* 1–12. doi:[10.1038/onc.2013.493](https://doi.org/10.1038/onc.2013.493)
- Nam HJ, van Deursen JM (2014) Cyclin B2 and p53 control proper timing of centrosome separation. *Nat Cell Biol* 16:535–549. doi: [10.1038/ncb2952](https://doi.org/10.1038/ncb2952)
- Oshima M, Oshima H, Kitagawa K et al (1995) Loss of Apc heterozygosity and abnormal tissue building in nascent intestinal polyps in mice carrying a truncated Apc gene. *Proc Natl Acad Sci USA* 92:4482–4486
- Perez-Castro aV, Shamanski FL, Meneses JJ et al (1998) Centromeric protein B null mice are viable with no apparent abnormalities. *Dev Biol* 201:135–143. doi:[10.1006/dbio.1998.9005](https://doi.org/10.1006/dbio.1998.9005)
- Rao CV, Yang Y, Swamy MV et al (2005) Colonic tumorigenesis in BubR1 $\pm$ Apc Min/+ compound mutant mice is linked to premature separation of sister chromatids and enhanced genomic instability. *Proc Natl Acad Sci USA* 102:4365–4370
- Rehen SK, McConnell MJ, Kaushal D et al (2001) Chromosomal variation in neurons of the developing and adult mammalian nervous system. *Proc Natl Acad Sci USA* 98:13361–13366. doi:[10.1073/pnas.231487398](https://doi.org/10.1073/pnas.231487398)
- Rehen SK, Yung YC, McCreight MP et al (2005) Constitutional Aneuploidy in the Normal Human Brain. 25:2176–2180. doi:[10.1523/JNEUROSCI.4560-04.2005](https://doi.org/10.1523/JNEUROSCI.4560-04.2005)
- Remeseiro S, Cuadrado A, Carretero M et al (2012) Cohesin-SA1 deficiency drives aneuploidy and tumorigenesis in mice due to impaired replication of telomeres. *EMBO J* 31:2076–2089. doi:[10.1038/emboj.2012.11](https://doi.org/10.1038/emboj.2012.11)
- Ricke RM, van Deursen JM (2013) Aneuploidy in health, disease, and aging. *J Cell Biol* 201:11–21. doi:[10.1083/jcb.201301061](https://doi.org/10.1083/jcb.201301061)
- Ried T (2009) Homage to Theodor Boveri (1862-1915): Boveri's theory of cancer as a disease of the chromosomes, and the landscape of genomic imbalances in human carcinomas. *Environ Mol Mutagen* 50:593–601. doi:[10.1002/em](https://doi.org/10.1002/em)
- Schvartzman J-M, Sotillo R, Benézra R (2010) Mitotic chromosomal instability and cancer: mouse modelling of the human disease. *Nat Rev Cancer* 10:102–115. doi:[10.1038/nrc2781](https://doi.org/10.1038/nrc2781)
- Shima N, Alcaraz A, Liachko I, et al (2007) A viable allele of Mcm4 causes chromosome instability and mammary adenocarcinomas in mice. *Nat Genet* 39:93–8. doi: [10.1038/ng1936](https://doi.org/10.1038/ng1936)
- Siegel JJ, Amon A (2012) New insights into the troubles of aneuploidy. *Annu Rev Cell Dev Biol* 28:189–214. doi: [10.1146/annurev-cellbio-101011-155807](https://doi.org/10.1146/annurev-cellbio-101011-155807)
- Silk AD, Zasadil LM, Holland AJ et al (2013) Chromosome missegregation rate predicts whether aneuploidy will promote or suppress tumors. *Proc Natl Acad Sci USA*. doi:[10.1073/pnas.1317042110](https://doi.org/10.1073/pnas.1317042110)
- Sotillo R, Hernando E, Díaz-Rodríguez E et al (2007) Mad2 overexpression promotes aneuploidy and tumorigenesis in mice. *Cancer Cell* 11:9–23. doi:[10.1016/j.ccr.2006.10.019](https://doi.org/10.1016/j.ccr.2006.10.019)
- Su LK, Kinzler KW, Vogelstein B et al (1992) Multiple intestinal neoplasia caused by a mutation in the murine homolog of the APC gene. *Science* (80-) 256:668–670
- Tang Y-C, Williams BR, Siegel JJ, Amon A (2011) Identification of aneuploidy-selective antiproliferation compounds. *Cell* 144:499–512. doi:[10.1016/j.cell.2011.01.017](https://doi.org/10.1016/j.cell.2011.01.017)
- Torres EM, Sokolsky T, Tucker CM et al (2007) Effects of Aneuploidy on Cellular Physiology and Cell Division in Haploid Yeast. *Science* (80-) 317:916–924. doi:[10.1126/science.1142210](https://doi.org/10.1126/science.1142210)
- Torres EM, Williams BR, Amon A (2008) Aneuploidy: cells losing their balance. *Genetics* 179:737–746. doi:[10.1534/genetics.108.090878](https://doi.org/10.1534/genetics.108.090878)

- Uren AG, Wong L, Pakusch M et al (2000) Survivin and the inner centromere protein INCENP show similar cell-cycle localization and gene knockout phenotype. *Curr Biol* 10:1319–1328
- Van Harn T, Fojier F, van Vugt M et al (2010) Loss of Rb proteins causes genomic instability in the absence of mitogenic signaling. *Genes Dev* 24:1377–1388. doi:[10.1101/gad.580710](https://doi.org/10.1101/gad.580710)
- Van Ree JH, Jeganathan KB, Malureanu L, van Deursen JM (2010) Overexpression of the E2 ubiquitin-conjugating enzyme UbcH10 causes chromosome missegregation and tumor formation. *J Cell Biol* 188:83–100. doi:[10.1083/jcb.200906147](https://doi.org/10.1083/jcb.200906147)
- Vecchione A, Croce CM, Baldassarre G (2007) Fez1/Lzts1 a new mitotic regulator implicated in cancer development. *Cell Div* 2:24. doi:[10.1186/1747-1028-2-24](https://doi.org/10.1186/1747-1028-2-24)
- Wang Z, Yu R, Melmed S (2001) Mice lacking pituitary tumor transforming gene show testicular and splenic hypoplasia, thymic hyperplasia, thrombocytopenia, aberrant cell cycle progression, and premature centromere division. *Mol Endocrinol* 15:1870–1879. doi:[10.1210/mend.15.11.0729](https://doi.org/10.1210/mend.15.11.0729)
- Wang Q, Liu T, Fang Y et al (2004) BUBR1 deficiency results in abnormal megakaryopoiesis. *Blood* 103:1278–1285. doi:[10.1182/blood-2003-06-2158](https://doi.org/10.1182/blood-2003-06-2158)
- Weaver BAA, Cleveland DW (2006) Does aneuploidy cause cancer? *Curr Opin Cell Biol* 18:658–667. doi:[10.1016/j.ceb.2006.10.002](https://doi.org/10.1016/j.ceb.2006.10.002)
- Weaver BAA, Bonday ZQ, Putkey FR et al (2003) Centromere-associated protein-E is essential for the mammalian mitotic checkpoint to prevent aneuploidy due to single chromosome loss. *J Cell Biol* 162:551–563. doi:[10.1083/jcb.200303167](https://doi.org/10.1083/jcb.200303167)
- Weaver BAA, Silk AD, Montagna C et al (2007) Aneuploidy acts both oncogenically and as a tumor suppressor. *Cancer Cell* 11:25–36. doi:[10.1016/j.ccr.2006.12.003](https://doi.org/10.1016/j.ccr.2006.12.003)
- Williams BR, Prabhu VR, Hunter KE et al (2008) Aneuploidy affects proliferation and spontaneous immortalization in mammalian cells. *Science* (80-) 322:703–709
- Wu G, Qiu X-L, Zhou L et al (2008) Small molecule targeting the Hec1/Nek2 mitotic pathway suppresses tumor cell growth in culture and in animal. *Cancer Res* 68:8393–8399. doi:[10.1158/0008-5472.CAN-08-1915](https://doi.org/10.1158/0008-5472.CAN-08-1915)
- Yu X, Minter-Dykhouse K, Malureanu L et al (2005) Chfr is required for tumor suppression and Aurora A regulation. *Nat Genet* 37:401–406. doi:[10.1038/ng1538](https://doi.org/10.1038/ng1538)
- Zhang D, Hirota T, Marumoto T et al (2004) Cre-loxP-controlled periodic Aurora-A overexpression induces mitotic abnormalities and hyperplasia in mammary glands of mouse models. *Oncogene* 23:8720–8730. doi:[10.1038/sj.onc.1208153](https://doi.org/10.1038/sj.onc.1208153)
- Zhang D, Shimizu T, Araki N et al (2008) Aurora A overexpression induces cellular senescence in mammary gland hyperplastic tumors developed in p53-deficient mice. *Oncogene* 27:4305–4314. doi:[10.1038/onc.2008.76](https://doi.org/10.1038/onc.2008.76)
- Zhang Y, Foreman O, Wigle DA et al (2012) USP44 regulates centrosome positioning to prevent aneuploidy and suppress tumorigenesis. *J Clin Invest* 122:4362–4374. doi:[10.1172/JCI63084DS1](https://doi.org/10.1172/JCI63084DS1)

Chromosomal Instability in Cancer Cells

Ghadimi, B.M.; Ried, Th. (Eds.)

2015, VII, 224 p. 39 illus. in color., Hardcover

ISBN: 978-3-319-20290-7