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| Deregulated Aurora B activity and its implications in cancer  |
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# Summary

Aurora B kinase, the enzymatic subunit of the chromosomal passenger complex, plays a pivotal role in the regulation of chromosome segregation and cytokinesis. Therefore, Aurora B activity is tightly regulated through modulating (1) gene expression, (2) activation, (3) localization and (4) degradation of Aurora B, and by (5) dephosphorylation of its substrates. Deregulation of Aurora B might play a role in cancer, since changes in Aurora B activity cause chromosome segregation errors and cytokinesis failure leading to aneuploidy, which is a hallmark of cancer. This thesis describes the regulation of Aurora B activity and reviews the evidence regarding a causal role for deregulation of Aurora B activity in tumors.

Heterozygous Aurora B knock-out mice are more prone to cancer development. Conversely, Aurora B mRNA and protein levels are frequently upregulated in human tumors. Indirect evidence which suggests that upregulation of Aurora B might contribute to tumor malignancy can however not be extrapolated to humans, and therefore a causal role for Aurora B upregulation in tumor development has not been established yet. Furthermore, the evidence regarding deregulation of Aurora B in human cancer is incomplete. For instance, it is still largely unknown whether the upregulation of Aurora B in cancer is caused by an increase in gene expression, a decrease in degradation or both. Additionally, the influence of deregulating Aurora B activity without changing Aurora B protein levels on tumor development is undetermined. Research should focus on unraveling these mentioned aspects regarding the link between deregulated Aurora B activity and tumor development. For now, the role of deregulated Aurora B activity in human cancer remains unclear.

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# Abbreviations

* APC Anaphase promoting complex
* CDE Cell cycle dependent element
* CHR Cell cycle gene homology region
* CIN Chromosomal instability
* CPC Chromosomal passenger complex
* FISH Fluorescence in situ hybridization
* FOXM1 Forkhead box M1
* IHC Immunohistochemistry
* INCENP Inner centromere protein
* H3-Ser10 Histone subunit 3, residue serine 10
* mRNA Messenger RNA
* qRT-PCR Quantitative reverse transcriptase polymerase chain reaction
* SNP Single nucleotide polymorphism
* WB Western blot
* WT Wild-type

# 1 Introduction

Tumor cells are characterized by chromosomal instability (CIN), or (whole) chromosome gains and losses. As a result, they generally encompass an abnormal karyotype, which is referred to as aneuploidy. A premature stage of aneuploidy in tumor cells could be tetraploidy, in which cells contain twice the amount of DNA [1,2]. The influence of whole-chromosome aneuploidy on tumor development is however still debated. While it might enhance genomic instability, it could additionally reduce the fitness of cells, thereby causing cell death (reviewed in [3-6]). Similar to structural variations, the contribution of whole chromosome aberrations to tumor development might actually depend on the exact karyotype, the cell type and the cellular environment.

Aneuploidy is a result of CIN which can be caused by a variety of defects, including a malfunctioning mitotic checkpoint. This checkpoint represses cell cycle progression until each sister chromatid pair is attached to two opposite mitotic spindle poles, so‑called amphitelic attachment or bi‑orientation. Incorrect attachments of the chromatids to the mitotic spindle poles (like merotelic attachments: one sister chromatid is attached to two opposite spindle poles) can contribute to aberrant chromosome segregation and aneuploidy [7-9]. Both chromosome bi-orientation and the mitotic checkpoint are governed by Aurora B kinase in the chromosomal passenger complex (CPC).

Aurora B kinase comprises the enzymatic subunit of the CPC, which further consists of inner centromere protein (INCENP), Borealin and Survivin. This complex ensures chromosomal stability during several steps of the M-phase (reviewed in [10-12]). Firstly, Aurora B governs chromosome bi‑orientation while localized at the centromere, by destabilizing the interaction between microtubule and kinetochores of non bi‑oriented chromosomes [10,13-17]. The unbound kinetochores subsequently prevent anaphase promoting complex/cyclosome (APC/C) activation, thereby inhibiting progression to anaphase (reviewed in [18]). Once the sister chromatids are attached to two opposite mitotic spindle poles, a tension arises across the centromere [19], which might spatially separate the substrates of Aurora B kinase from the phosphorylating activity of Aurora B [19] The interaction between microtubule and kinetochores in then stabilized, resulting in APC/C activation and anaphase onset [18]. During anaphase, the CPC is removed from the centromeres and it subsequently travels to the spindle midzone before accumulating at the midbody during telophase [10,12,20-24]. At these cellular locations, Aurora B plays a crucial role in the late stages of mitosis and cytokinesis (reviewed in [10-12]), by regulating central spindle formation [25-29], furrow ingression [30] and abscission [31,32]. Additionally, Aurora B maintains condensation of the chromosomes [33,34]. This suppresses chromosome segregation errors [33,34], possibly by enabling efficient removal of chromosomes from the cleavage plane [35].

While Aurora B normally ensures chromosomal stability, both upregulation and downregulation of Aurora B protein levels can cause chromosome segregation errors and aneuploidy [29,36,37]. Since chromosomal stability is disrupted in cancer, Aurora B might play a role in tumor formation or malignancy. Moreover, Aurora B might even be a valuable target for cancer treatment and inhibitors of Aurora B are currently being tested in the clinics (reviewed in [38]). Improving our understanding of the link between cancer and deregulation of Aurora B is therefore important, since it will provide insight into the consequences of inhibiting Aurora B in tumor patients. Here, we review the regulation of Aurora B kinase and the possible contribution of Aurora B deregulation to aneuploidy and tumor formation.

# 2 Aurora B is tightly regulated

To understand how deregulation of Aurora B activity might contribute to tumor development, it is important to comprehend Aurora B regulation (depicted in Figure 1). Both Aurora B protein levels [23,39] and Aurora B activity [23,40,41] peak during mitosis and rapidly decrease after cytokinesis. Hence, Aurora B is regulated through influencing gene expression (discussed in detail in 2.2), activation of kinase activity and degradation (Figure 1). Activity of Aurora kinases additionally depends on cellular localization (Figure 1). Altering only one amino acid of Aurora A kinase changes the cellular localization of Aurora A into a localization similar to Aurora B and can compensate for depletion of Aurora B [42,43]. This suggests that Aurora A might be able to phosphorylate substrates of Aurora B and that cellular localization of Aurora kinases is crucial in regulating Aurora kinase function [42,43]. Finally, Aurora B activity is antagonized by phosphatases which dephosphorylate substrates of Aurora B (Figure 1) [44]. Currently, at least 40 proteins have been identified which govern Aurora B activity (Table 1)(reviewed in detail in [10,11,45]).



**Figure 1. Five general approaches of Aurora B regulation**

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## 2.1 Regulation of Aurora B activity by the CPC proteins

The CPC proteins are especially important in regulation of Aurora B activity. Firstly, Aurora B kinase initially becomes moderately active by interaction with INCENP [46]. This triggers Aurora B to autophosphorylate at threonine 232 [47]. Subsequently, Aurora B phosphorylates two adjoining serine residues in the C‑terminus of INCENP, which elicits full activation of Aurora B [46-48]. The second phosphorylation step is catalyzed by surrounding Aurora B enzymes, suggesting that activation of Aurora B is dependent on Aurora B concentration [46,49].

Additionally, all subunits of the CPC are involved in indirect regulation of Aurora B activity by modulating CPC localization. This defines which substrates of Aurora B are in close proximity of the active kinase domain. Initial centromeric enrichment of the CPC relies on a hydrophobic interaction between helices of the non‑enzymatic CPC proteins INCENP, Borealin and Survivin [50,51]. This

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| **Table 1. Overview of proteins that affect Aurora B kinase activity** |
| **Protein** | **Type of**  | **References** |
| **regulation \*** |
| Aurora B |   |   | 2,3 |  [46,47,54] |
| INCENP | ( | Inner centromere protein ) | 2,3 |  [46,48,51,67-69] |
| Borealin |   |   | 3 |  [51,70] |
| Survivin |   |   | 2,3 |  [45,51,53,54,71-73] |
| TD-60 | ( | Telophase disk 60 kDa ) | 2,3 |  [74,75] |
| FOXM1 | ( | Forkhead box M1 ) | 1 |  [63,64] |
| E2F-1 | ( | E2 transcription factor 1 ) | 1 |  [61,76] |
| Brd4 | ( | Bromodomain protein 4 ) | 1 |  [77] |
| Chk1 | ( | Checkpoint kinase 1 ) | 2 |  [78] |
| Mst1 | ( | Mammalian sterile 20-like kinase 1 ) | 2 |  [79] |
| HDAC3 | ( | Histone deacetylase 3 ) | 2 |  [80] |
| Bub1 | ( | Budding uninhibited by benzimidazoles 1 ) | 2,3 |  [55,57,81,82] |
| Bub1B | ( | Budding uninhibited by benzimidazoles 1 beta ) | 2,3 |  [83,84]  |
| Mps1 | ( | Monopolar spindle 1 kinase ) | 2,3 |  [85,86] |
| TOP2 | ( | Topoisomerase II ) | 2,3 |  [87] |
| CENP-A | ( | Centromere protein A ) | 2,3 |  [83] |
| AURKA | ( | Aurora A kinase ) | 2,3 |  [83] |
| Sgo1 | ( | Shugoshin 1 ) | 3 |  [56] |
| Sgo2 | ( | Shugoshin 2 ) | 3 |  [56,57,88,89] |
| Haspin |   |   | 3 |  [53-55] |
| Cdk1 | ( | Cyclin-dependent kinase 1 ) | 3 |  [56] |
| PIAS3 | ( | Protein inhibitor of activated STAT, 3 ) | 3 |  [90] |
| SENP2 | ( | Sentrin-specific protease 2 ) | 3 |  [90] |
| MLL5 | ( | Mixed lineage leukemia 5 ) | 3 |  [91] |
| Plk1 | ( | Polo-like kinase 1 ) | 3 |  [72] |
| MKlp2 | ( | Mitotic kinesin-like protein 2 ) | 3 |  [59] |
| Cdc14 | ( | Cell division cycle 14 ) | 3 |  [59,68,92] |
| Nup50 | ( | Nucleoporin 50 ) | 3 |  [93] |
| Cul3 | ( | Cullin 3-based E3 ligase ) | 3 |  [94] |
| KLHL9 | ( | Kelch-like protein 9 ) | 3 |  [94] |
| KLHL13 | ( | Kelch-like protein 13 ) | 3 |  [94] |
| KLHL21 | ( | Kelch-like protein 21 ) | 3 |  [95] |
| CHMP4C | ( | Charged multivesicular body protein 4C ) | 3 |  [70] |
| VCP | ( | Valosin containing protein ) | 3 |  [96-98] |
| UFDIL | ( | Ubiquitin fusion degradation 1 like ) | 3 |  [97] |
| NPLOC4 | ( | Nuclear protein localization 4 homolog ) | 3 |  [97] |
| APC/C | ( | Anaphase-promoting complex/cyclosome ) | 4 |  [39] |
| Cdh1 | ( | Cadherin type 1 ) | 4 |  [39] |
| BARD1 | ( | BRCA1-associated ring domain protein 1 ) | 4 |  [99] |
| PP1 | ( | Protein serine/threonine phosphatase type 1 ) | 2,5 |  [44,100-103] |
| PP2A | ( | Protein serine/threonine phosphatase type 2A ) | 2,5 |  [44,104,105] |
| PPP1R7 | ( | protein phosphatase 1, regulatory subunit 7 ) | 2,5 |  [100] |
| EB1 | ( | End-binding protein 1 ) | 2,5 |  [104] |
| FLOT1 | ( | Flotillin-1 ) | Unknown |  [106] |
| \* As listed in figure 1 |  |  |

indirectly connects Aurora B through Survivin [52-55] and Borealin [56,57] to two modified histone subunits that reportedly overlap at the centromere: phosphorylated histone residues H3T3 and H2AS121 [53-55,57]. Aurora B likely promotes the phosphorylation of these two histone residues itself, by phosphorylation of Haspin (involved in H3T3 phosphorylation [58]) and recruitment of Bub1 (involved in H2AS121 phosphorylation[57]) [37,54]. Subsequent translocation of the CPC to the spindle midzone and midbody is also governed by Aurora B, as well as INCENP. The relocalization to the central spindle mainly relies on the interaction of these two CPC subunits with Mklp2 [59]. Both kinase activity of Aurora B and dephosphorylation of INCENP might also influence relocalization to the central spindle [10].

## Gene expression of Aurora B

As mentioned previously, Aurora B activity is not only regulated at the protein level. Messenger RNA (mRNA) levels of Aurora B also change throughout the cell cycle and reach the highest level during late G2 and M‑phase [23,60-62]. This fluctuation in mRNA levels is similar to the fluctuation in Aurora B protein levels [23,39], indicating that the activity of Aurora B is also governed by regulation of gene expression. Our understanding of this type of regulation is however far less evolved.

*AURKB* is encoded on the reverse strand of chromosome 17. The promoter of *AURKB* contains two elements that are important in regulation of Aurora B gene expression during the cell cycle: the so‑called cell cycle dependent element (CDE) and the cell cycle gene homology region (CHR) [61]. These two elements, especially the CHR, effectuate a decrease in gene expression of Aurora B during the growth and synthesis phases of the cell cycle [61]. Aurora B transcription can also be activated from the promoter. For example, transcription factor Forkhead box M1 (FOXM1) binds in the promoter region of Aurora B and activates gene expression of Aurora B [63-65,65]. This transcription factor has also been linked to gene expression regulation of several other M-phase proteins, including Survivin and CENPA [63,66].

# 3 Implications of Aurora B in tumor formation

Aurora B mRNA and protein levels are elevated in human cancer (Table 2). While Aurora B normally ensures chromosomal stability, deregulation of Aurora B protein levels can cause chromosome segregation errors and aneuploidy [29,36,37]. Since chromosomal stability is disrupted in cancer, Aurora B might play a role in tumor formation or malignancy.Actually, chromosome segregation errors can give rise to structural variations in the genome by causing double-strand DNA breaks [107], thereby facilitating genomic instability indirectly. As mentioned previously however, the influence of aneuploidy on tumor development is still debated. The role of Aurora B deregulation in tumor development and malignancy is therefore not yet fully understood.In the following sections, the link between Aurora B levels and cancer will be discussed further.

## 3.1 Aurora B deregulation can cause aneuploidy, which might contribute to tumor formation

### 3.1.1 Upregulation of Aurora B

Overexpression of Aurora B results in lagging chromosomes, chromosome bridges, CIN, multinuclear cells and eventually aneuploidy [36,62]. It increases the amount of near- diploid cells in p53 deficient hamster cells [36], indicating that it might directly contribute to chromosome gains and losses. Furthermore, upregulation of Aurora B induces tetraploidy and near-tetraploidy [36,62], which suggests that an increase in Aurora B promotes tetraploidization, followed by CIN. Although the precise cellular mechanisms that contribute to the phenotype described above are largely unknown, it has been suggested that Aurora B overexpression has a dominant-negative effect and therefore the consequences of Aurora B upregulation are similar to the consequences of downregulation [62]. Furthermore, an increase in phosphorylation of histone 3 at serine 10 has been implicated [36]. Overexpression of Aurora B additionally decreases transcriptional activity of p53 through phosphorylation of the DNA binding domain [108,109]. Since p53 is known to guard genomic integrity, the inhibition of p53 by Aurora B overexpression could enhance genomic instability.

An increase in Aurora B kinase activity thus results in lagging chromosomes and chromosomal instability, which in some cases eventually enables cells to exit mitosis without proliferation. As such, upregulation of Aurora B can give rise to aneuploidy which might play a role in tumor formation (Figure 2). In mice, overexpression of kinase Bub1 enhances activation of Aurora B kinase, which is associated with increased aneuploidy and increased susceptibility to tumor formation [81,82]. This phenotype can be rescued by chemical inhibition of Aurora B [81,82], suggesting that an increase in Aurora B activity can contribute to Bub1 induced predisposition to tumor development. It is however not entirely clear whether Aurora B itself causes an increased susceptibility to tumor formation, or whether another factor is responsible for this phenotype and inhibition of Aurora B inhibits this other factor.

There are other indications which suggest that Aurora B overexpression itself might be involved in tumor development or tumor malignancy. Grafting mice with cells with elevated Aurora B protein levels due to inhibition of Aurora B degradation augments tumor formation in comparison to mice treated with cells with wild-type (WT) Aurora B levels [110]. Similarly, injecting hamsters subcutaneous with p53 knock-out cells transfected with Aurora B kinase facilitates tumor formation and metastazation in comparison to subcutaneous injection with WT p53 knock-out cells [36]. Moreover, an increase in Aurora B gene expression in these p53 knock-out cells correlates with an increase in tumor malignancy after subcutaneous injection in hamsters [36]. These studies combined suggest that upregulation of Aurora B activity might accelerate tumor malignancy. Importantly however, they do not prove that Aurora B is first upregulated and then elicits tumor formation. Therefore, the evidence is indirect and does not prove a causal role for Aurora B upregulation in tumor formation.

### 3.1.2 Downregulation of Aurora B

As mentioned previously, Aurora B is involved in destabilizing incorrect microtubule attachments, the mitotic checkpoint and cytokinesis. Inhibition of Aurora B therefore results in lagging chromosomes, override of the mitotic checkpoint, chromosome segregation errors, multinuclear cells and eventually aneuploidy [29,37,111]. Inhibition of Aurora B kinase activity predominantly increases multinuclearity of cells [29,37,111]. At the molecular level, depletion of Aurora kinase activity is associated with alterations in the localization of BubR1, Bub1, MCAK, Mad2 and CENP‑E [14,16,29,37] and a reduction in the phosphorylation of Mps1 and Rb [86,112].

A decrease in Aurora B kinase activity thus results in a weakened mitotic checkpoint and lagging chromosomes during anaphase, which in some cases eventually enables cells to exit mitosis without proper chromosome segregation. As such, downregulation of Aurora B can give rise to aneuploidy which might contribute to tumor formation (Figure 2). In fact, there is convincing evidence which demonstrates that downregulation of Aurora B increases tumor formation *in vivo*. Although heterozygous knock-out of the Aurora B kinase gene in mice (AurkB+/- mice) can be rescued by Aurora C, it results in a significant increase in susceptibility to tumor formation [113]. Approximately 11% of WT mice had developed tumors after two years in comparison to 70% of mice with heterozygous knock‑out of Aurora B*.* Heterozygous disruption of Aurora B especially increases susceptibility to benign papillomas in the skin and adenocarcinomas in liver and pituitary gland [113]. The increase in tumor susceptibility is accompanied by an increase in lethality. All AurkB+/- mice decease within 26 months after birth, while over 70 percent of WT mice are still alive at this age [113]. Moreover, 16% of WT mice survive for more than 30 months [113]. Downregulation of Aurora B thus predisposes mice to tumor formation and subsequent death.

## 3.2 Deregulation of Aurora B in human cancer

Aurora B mRNA and protein levels are predominantly upregulated in many different tumor types including colorectal cancer, prostate cancer and lung cancer (Table 2). Upregulation of Aurora B expression is linked to a decrease in life‑expectancy of cancer patients [114-122] and correlates with several malignant tumor characteristics, like a late tumor stage [116-118,121,123,124] and the formation of metastases [117,122,125,126]. An increase in Aurora B levels has also been linked to a reduced efficacy of treatment, including surgical removal of a tumor [118,120,127-129]. Upregulation of Aurora B has thus been correlated with several malignant tumor characteristics. This could indicate that Aurora B might be able to contribute to tumor development. Alternatively, Aurora B could merely be a biomarker for malignant cell proliferation.

In fact, the increase in Aurora B mRNA and protein levels correlates with an increase in proliferation (Table 2). Cells which overexpress Aurora B are often also characterized by an upregulation of Ki-67 [116,130,131], which is a marker for cell proliferation [132]. Additionally, overexpression of Aurora B is accompanied by overexpression of other cell cycle regulators and M‑phase proteins, including Aurora A, Survivin and CDK6 [124,133,134]. Upregulation of Aurora B and an increase in proliferation are thus tightly linked. This raises the question whether Aurora B causes this effect, or whether Aurora B is simply upregulated as a result of increased proliferation. Actually, the proliferative rate can affect Aurora B protein levels. Reducing proliferation in thyroid carcinoma cell lines by serum starvation reduces mRNA levels of Aurora B significantly [135]. This reduction in Aurora B expression



**Figure 2. An alteration in Aurora B levels results in aneuploidy,
which might even contribute to tumor formation.**

Both downregulation and upregulation of Aurora B activity cause aneuploidy. Downregulation of Aurora B induces override of the mitotic checkpoint and multinuclear cells as a result of altered localization and phosphorylation of several (kinetochore and centromere) proteins. This eventually leads to aneuploidy. Downregulation of Aurora B has additionally been linked to an increased susceptibility to tumor formation in mice. Upregulation of Aurora B causes an increase in chromosome bridges and multinuclear cells through altered phosphorylation of H3‑Ser10 and possibly p53. This eventually leads to aneuploidy. Currently, a causal link between upregulation of Aurora B and tumor formation has not been confirmed.

is restored once proliferation is induced again by adding fresh serum [135]. This indicates that changes in Aurora B levels can be induced by changes in proliferation. It therefore suggests that Aurora B overexpression could be a marker for malignant cell proliferation in (a subset of) tumors, rather than a cause of tumor development.

In any case, Aurora B kinase levels are upregulated in human cancer. As mentioned before, Aurora B activity is regulated by modulating gene expression, activation, localization, and degradation of Aurora B, as well as by antagonizing Aurora B activity through dephosphorylation of its substrates (Figure 1). The increase in Aurora B mRNA and protein levels could thus be attained by two alterations in the regulation of Aurora B: gene expression and degradation. In fact, two oncogenic changes might be able to contribute to an unbeneficial increase in Aurora B gene expression. Firstly, protein levels of transcription factor FOXM1 are elevated in several tumor types [66,136-140]. This could in theory facilitate an increase in Aurora B gene expression, although the upregulated FOXM1 levels in tumors have not been directly linked to an increase in Aurora B. Gene expression of Aurora B might alternatively increase as a result of *AURKB* gene amplification or partial chromosome duplication, although this is a rare event in cancer [141,142]. However, these two explanations presumably do not account for all upregulation of Aurora B in tumor cells. Aurora B gene expression could, for instance, increase as a result of epigenetic changes or mutations in regulatory sequences (e.g. the promoter) as well, but the role of these alterations in human cancer is unclear. Moreover, there is currently no direct evidence regarding changes in Aurora B degradation in tumors. It therefore remains largely unknown how the elevated levels of Aurora B in tumors are generated.

In addition to alterations in Aurora B levels, Aurora B activity might also change in cancer patients due to alterations in activation and localization of Aurora B and dephosphorylation of Aurora B substrates (Figure 1). Although convincing evidence regarding the link between cancer and these other three types of regulation is also lacking, there are some rare indirect indications in literature. For example, Adenomatous polyposis coli mutation in colon cancer upregulates Aurora B activity through a decrease in downregulation of Survivin [143]. Survivin can both enhance Aurora B activity and affect localization of Aurora B *in* vitro, but does not alter Aurora B gene expression [71]. As such, upregulation of Survivin might directly enhance the activity of Aurora B in colon cancer. Secondly, upregulation of protein levels of catalytic subunit PP1γ correlates with increased malignancy of breast cancer [144]. This upregulation could antagonize the upregulation of Aurora B and could therefore indirectly affect Aurora B activity on mitosis. Finally, silent single nucleotide polymorphism (SNP) 885A>G (either hetero- or homozygous) has been linked to a significant decrease in life expectancy of metastatic colorectal cancer patients, without causing alterations in Aurora B gene expression or amino acid sequence [119,145]. This SNP also predisposes women to breast cancer [145]. Since it does not cause an amino acid change or an alteration in splicing, it might affect the stability of the mRNA or translation efficiency. Interestingly, 885A>G in *AURKB* is in strong linkage disequilibrium with 893G>A [119,145], indicating that the SNPs are associated in a non‑random manner. This rare SNP (perhaps too rare to reach significance) is predicted to alter the secondary structure of Aurora B [145]. Either of these SNPs in *AURKB* might thus alter Aurora B activity, without changing Aurora B gene expression.

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| **Table 2. Aurora B gene, mRNA and protein levels in human cancer** | **Reference** | [141] | [146] | [147] | [133] | [122] | [116] | [115] | [146] | [126] | [148] | [118] | [120] | [114] | [121] | [131] | [117] | [128] | [124] | [130] | [123] | [149] | [150] | [135] |  |  |  |  |
| **Proliferation** | Unknown | Increased | Unknown | Unknown | Unknown | Increased | Unknown | Increased | Unknown | Unknown | Unknown | Increased | Unknown | Unknown | Increased | Unknown | Unknown | Unknown | Increased | Increased | Unknown | Increased | Unknown |  |  |  |  |
| **Clinical findings** | *AURKB* gene amplification in tumors increases Aurora B mRNA levels | No increase in mRNA levels, but increase in Aurora B protein levels | (Nuclear) Aurora B is upregulated in tumor samples | More than 10-fold increase in mRNA levels of Aurora B | (Nuclear) expression of Aurora B is increased in tumor samples | Increased Aurora B mRNA correlate with tumor grade | Aurora kinase protein levels correlate with tumor grade | Increased *AURKB* copy number and Aurora B mRNA and protein levels | Expression of Aurora B is increased in tumor samples | Aurora kinase B is upregulated, predominantly in anaplastic tumors | Aurora kinase B protein levels are upregulated in 61% of tumors | High protein levels of Aurora B are found in 55% of tumors | Aurora B mRNA and protein levels are increased in tumor samples | High Aurora B expression in 48% of samples | Aurora B is upregulated in differentiated and undifferentiated tumors | Aurora B mRNA and protein levels are increased in 34% of patients | Aurora B protein expression is significantly increased | Higher Aurora B mRNA in aggressive tumors | High percentage of Aurora B positive cells | Increased (nuclear) Aurora B protein levels in advanced tumor stages | Aurora B mRNA increased (80%)/decreased (20%); protein 10x increased | Aurora B mRNA and protein levels are increased in anaplastic tumors | Increase in Aurora B mRNA and protein levels in tumors |  |  |  |  |
| **Sample** | Tumor | Cell line | Tumor | Tumor | Tumor | Tumor | Tumor | Cell line | Tumor | Tumor | Tumor | Tumor | Tumor | Tumor | Tumor | Tumor | Tumor | Tumor | Tumor | Tumor | Tumor | Tumor | Tumor |  |  |  |  |
| **Method\*** | FISH; qRT-PCR | qRT-PCR; WB | IHC; WB | qRT-PCR | IHC | IHC; RT-PCR; WB | IHC | FISH; qRT-PCR; WB | IHC | IHC | qRT-PCR | IHC | qRT-PCR; WB | IHC | IHC | WB; qRT-PCR | IHC | Microarray | IHC | IHC | qRT-PCR; WB | IHC; RT-PCR | qRT-PCR; WB | \* FISH = fluorescence in situ hybridization |  |  qRT-PCR = Quantitative reverse transcriptase PCR |  |
| **Tumor type** | Acute myeloid leukemia | Barett's cancer | Cervical cancer | Chronic lymphocytic leukemia | Colorectal carcinoma | Endometrial carcinoma | Endometrial carcinoma | Esophageal squamous cell cancer | Gastric cancer | Hepatocellular carcinoma | Hepatocellular carcinoma | Laryngeal carcinoma | Lung carcinoma | Neck squamous cell cancer | Oral squamous cell cancer | Ovarian carcinoma | Ovarian carcinoma | Pleural mesotheliomas | Prostate cancer | Prostate cancer | Testicular germ cell tumour | Thyroid carcinoma | Thyroid carcinoma |  IHC = Immunohistochemistry |  WB = Western blot |

# 4 Role of Aurora B in human cancer remains unclear

After reviewing the literature on a possible link between tumor formation and Aurora B deregulation, we believe that the precise role of Aurora B deregulation in tumor formation remains to be elucidated for several reasons. Firstly, although downregulation of Aurora B predisposes mice to the development of cancer [113], this seems to be irrelevant in human cancer in which Aurora B mRNA and protein levels are predominantly upregulated (Table 2). Conversely, the role of Aurora B upregulation in tumor formation has not been established completely. Subcutaneous injection of cells which overexpress Aurora B augments tumor development and malignancy in mice and hamsters [36,110], which indirectly proves that upregulation of Aurora B might contribute to tumor formation. However, upregulation in the subcutaneously injected cells is generated through transfection of *AURKB* in one of the studies, which resembles an amplification of the Aurora B kinase gene. This differs from Aurora B upregulation in human tumors, in which *AURKB* itself is rarely amplified. Moreover, the transfected *AURKB* gene is inserted randomly, indicating that regulation of gene expression might also differ from normal *AURKB* gene expression regulation. The other study describes elevated levels of a non-degradable form of Aurora B, which is entirely different from human tumors in which Aurora B has not been reported to be mutated. Finally, the cells that were subcutaneously injected have previously adapted to cell culture conditions. Cells that would give rise to a tumor in the human body have obviously not adapted to these conditions. Hence, the evidence regarding a possible role for Aurora B upregulation in tumor formation has been generated in a system that is very different from human tumor formation. It is therefore not possible to extrapolate these results to tumor formation in humans. Consequently, it remains to be elucidated whether Aurora B upregulation can cause tumor formation. Furthermore, there is an important difference between the ability to cause tumor formation and actually causing tumor formation. Although downregulation of Aurora B certainly predisposes mice to tumor formation [113] and upregulation of Aurora B might contribute to tumor formation as well [36,81,82,110], there is no conclusive evidence which proves that deregulation of Aurora B activity actually causes tumor formation in humans. Therefore, the role of deregulated Aurora B in cancer remains unclear.

Furthermore, actual evidence concerning deregulation of Aurora B in human tumors is incomplete. It remains unclear, for example, whether epigenetic alterations and changes in degradation of Aurora B play a role in the oncogenic upregulation of Aurora B levels. Additionally, the influence of possible changes in Aurora B activity without changes in Aurora B protein levels on tumor development is currently unknown. Aurora B activity is also governed by modulating activation and localization and by dephosphorylation of its substrates. These alterations could diminish the effect of increasing Aurora B levels by decreasing Aurora B activity, or they could further enhance an increase in Aurora B activity by increasing, for instance, activation of Aurora B. To completely comprehend deregulation of Aurora B in tumors, it is therefore important to research whether Aurora B activity is altered through mechanisms other than changing Aurora B levels as well.

In conclusion, we believe that the evidence regarding a link between Aurora B deregulation and tumor development is incomplete. Research should be conducted on the causal role of Aurora B in tumor formation and the types of deregulation of Aurora B in tumors. Then, a more firm statement can be generated regarding the role of Aurora B deregulation in cancer.

# 5 Future directions

Aurora B is predominantly upregulated in human cancer and there is no conclusive evidence which confirms whether this upregulation is a cause or a consequence of malignancy. Research on the CPC should therefore aim at elucidating the effect of Aurora B upregulation on tumor development. In 2002, it was first reported that subcutaneous injection of cells which overexpress Aurora B contributes to the development of tumors [36], indicating that upregulation of Aurora B might cause tumor development. A transgenic animal which confirms these implications has however not been reported since then. To circumvent possible embryonic lethality, Aurora B overexpression could be induced at a later age in a specific tissue through the Cre‑Lox recombinase system [151]. Tumor incidence of animals treated with tamoxifen should be compared to tumor incidence of similar animals without tamoxifen treatment. Importantly, this approach will not mimic true cancer development, since *AURKB* is rarely amplified in human tumors. It will however finally generate definite evidence regarding a possible causal role of Aurora B overexpression in tumor development.

To establish whether Aurora B deregulation can cause tumor formation in humans, the effect of SNPs 885A>G and 893G>A on Aurora B activity should also be determined. As mentioned previously, silent SNP 885A>G (either hetero- or homozygous) correlates with a significant decrease in life expectancy of metastatic colorectal cancer patients, without changing Aurora B gene expression [119]. More importantly, this SNP also predisposes women to breast cancer [145]. In other words, this SNP can directly contribute to an increased susceptibility to tumor formation in humans. Despite the fact that this SNP in theory does not alter Aurora B protein structure [145], it would therefore be interesting to test the effect of this SNP (and 893G>A, an uncommon SNP which is predicted to change the secondary structure of Aurora B and which is in linkage disequilibrium with 885A>G [145]) on Aurora B activity *in vitro*. If either of the SNPs affects Aurora B activity *in vitro*, this experiment would finally demonstrate a causal/contributing role of Aurora B deregulation in human tumor development.

Finally, some more insight needs to be gained on deregulation of Aurora B in human cancer. Additional mechanisms of increasing gene expression of Aurora B in tumors should for example be clarified. Firstly, possible alterations in epigenetic marks and mutations in the regulatory sequences of Aurora B should be examined in tumor cells. The influence of chromosome 17 amplification in breast cancer patients [152] on Aurora B gene expression should also be measured, to determine whether whole‑chromosome amplifications can also induce upregulation of Aurora B. Finally, it is important to establish whether Aurora B activity is deregulated in human cancer by mechanisms other than modulating gene expression (Figure 1). Both cellular localization of Aurora B throughout the cell cycle and protein levels of Aurora B regulators (Table 1) should therefore be determined in human tumor cells.

All of the described experiments combined will provide information regarding the link between deregulation of Aurora B activity and malignant cellular changes involved in cancer, including increased proliferation. As mentioned previously, Aurora B might be a valuable target for cancer treatment. Improving our understanding of the role of deregulation of Aurora B in tumor development and malignancy is important, since it will improve our understanding of consequences of inhibiting Aurora B in tumor patients. At least some of these additional experiments will thus have to be performed, in order to adequately predict the risk of Aurora B inhibition as a cancer treatment.

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