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Cdk1, Plks, Auroras, and Neks: The Mitotic Bodyguards

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Introduction

"O*mnis cellula e cellula,*" in 1858, an important dogma in cell biology was born, when Rudolf Virchow established that every cell must derive from a preexisting cell. And indeed cell division is the only way for life to expend, it is also the way for immortalization, and unfortunately when uncontrolled also the way for cancer. But unrevealing mechanisms leading to cell division took quite a while. How does a mother cell divide to give two daughters? This is known as the cell cycle, which describes a series of events that insures faithfully transition of the genetic information from one cell generation to the next. These dividing mechanisms have been conserved throughout evolution; they underlie growth and development in all living organisms and are central to their heredity and evolution.

In eukaryotic cells, the cell cycle was first described as two distinct phases: interphase and mitosis that just precedes cell division (Fig. 1). The interphase was later on divided into three phases, S-phase standing for DNA synthesis surrounded by two G-phases G1 and G2 standing for Gap-phases. Fully described by Walter Flemming in 1882, mitosis remains the most spectacular and sophisticated part of the cell cycle. In less than an hour, the mother cell organizes a complex machine aim to separate its genetic information and all its subcellular components into two identical sets that will be inherited by the two daughter cells. If mitosis proceeds without any error it eventually ends up with cytokinesis corresponding to the physical separation of the two daughter cells. Theodor Boveri predicted errors during mitosis to be at the origin of cancer in 1902. Hundred years later the scientific community is still debating on whether or not this might be true. The coordination of progression through mitosis is mainly orchestrated by protein phosphorylation insured by several serine/threonine kinases. In this short review we will focus on the four main mitotic kinase families: the cyclin-dependent kinase: Cdks, the polo-like kinases: Plks, the Aurora kinases, and the NIMA-related kinases: Neks.

"Cyclin-dependant kinases," Cdks that must associate to a cyclin to become active kinases are key regulators of cell cycle progression. There are now about 12 Cdks; the first one Cdk1 (or cdc2) has long been considered as THE cell cycle master kinase, thought to be responsible for all cell cycle transitions (1). This is true

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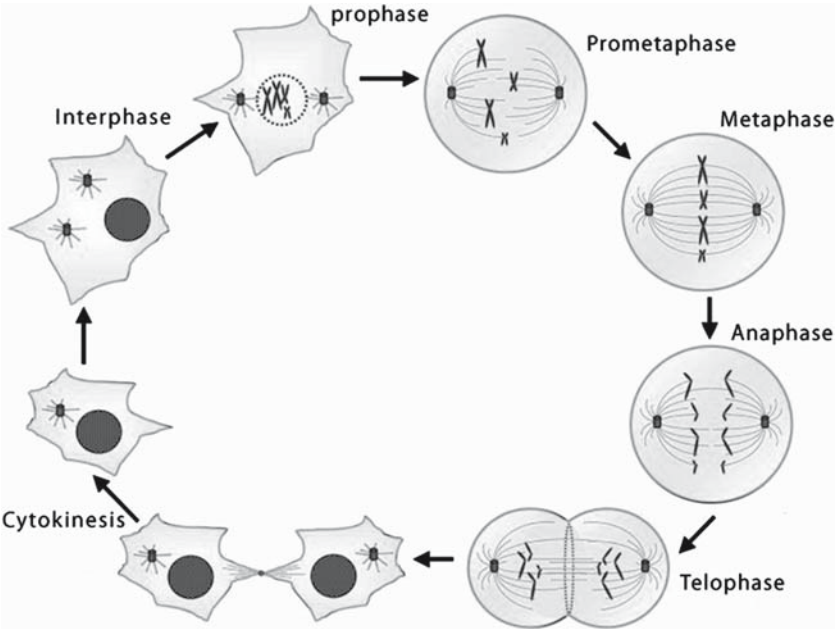

Fig. 1 The different phases of the mitosis

in yeast where Cdk1 kinase activity is required for the G1/S and the G2/M transition (2). In mammalian cell, however, Cdk1 activity is only required for the G2/M transition (3). Cdk1 binds to cyclin A, cyclin B, or Ringo to become an active kinase (4, 5).

The "Polo-like kinases," Plks form a family of four different proteins that regulates many aspects of the cell cycle progression. They all share small conserved domains named polo-box required for protein localization. Only Plk1 that is the most extensively studied is a true mitotic kinase homolog to the *Drosophila* polo kinase (6). Plk2, Plk3, and Plk4 are more likely involved only in interphase. However, Plk4 activity is required for centriole duplication, an event that must be achieved before entering mitosis, and necessary to assemble the bipolar mitotic spindle (7).

Aurora kinases were first identified in *S. cerevisae* and *Drosophila* (8, 9). Yeast cells possess only one Aurora-related kinase, invertebrates such *Drosophila* and *C. elegans* have two (A and B type) and mammals have three, named Aurora A, B, and C (10). From an evolution point of view, the A and B types have evolved from a common ancestor, while C type has evolved from the B type (11). Consequently, Aurora A has distinct functions while Aurora B and C share same functions, though all three kinases are involved in the control of many processes required for mitosis.

"NIMA-related kinases," Neks belong to a very large family of protein kinases with 13 different Nek proteins in human, from Nek1 to Nek11 (Nek2A and Nek2B, and Nek11L and Nek11S) (12). The belonging to the Nek family is defined by the

sequence homology with the kinase NIMA (never in mitosis A), a true *Aspergillus nidulans* mitotic kinase (13). However, not all of the Nek kinases are involved in mitosis (14). Nek2 is the most studied of all; its activity is required for centrosome behavior and for cytokinesis (15, 16).

During the interphase, the cell's nucleus is well defined, with two pairs of centrioles adjacent to the nucleus. At the end of the interphase, the genome has been duplicated but the chromosomes are not distinguishable. When prophase starts, the nucleoli disappear and the chromatin starts to coil and fold into observable chromosomes, the spindle forms and the centrosomes move apart. During prometaphase, the nuclear membrane breaks down and some of spindle microtubules attach to sister chromatids at the kinetochores. The microtubules start to deplace the chromatid pairs to form a metaphase plate. At the metaphase, the chromosomes have moved to the center of the dividing cell along the metaphase plate. Identical chromatids are attached to kinetochore fibers radiating from opposite ends of the parent cell. The sister chromatids begin to separate at the anaphase when the spindle microtubules pull separating chromosomes to opposite poles. During telophase, daughter nuclei begin to assemble with nuclear envelopes appearing around chromosomes. Nucleoli reappear and chromosomes decondense. The last step of mitosis is the cytokinesis step. It occurs when a contractile ring of actin and myosin filaments constricts the plasma membrane at the equator, triggering the physical division of the two daughter cells.

To Get Ready for Mitosis. Mitosis comprises many complex events that must be accomplished in less than an hour. The length of a human full cell cycle is approximately 24 h during which a dividing cell is preparing itself to enter mitosis. First of all the cell must have replicated its DNA (S phase) and possess two full copies of its genome (G2 phase). Second, the cell must also have duplicated its centrosome and possess two centrosomes (four centrioles). These centrosomes then need to go through a maturation process, meaning that proteins involved in mitotic microtubule nucleation, such as γ-tubulin for instance, must have been recruited to the centrosome before cells may enter mitosis.

Prophase: Leaving the Starting Blocks. During the prophase stage, the chromatin start to condense to form well-defined chromosomes, each chromosome consists of two sister chromatids connected at the level of their centromeres. While centrosome maturation is continuing during prophase, duplicated centrosomes must have separated and started to migrate around the nucleus to reach opposite position (the two centrosomes are now separated by the nucleus). By the end of prophase, the nuclear membrane starts to breakdown.

Prometaphase: A Cell Without Nucleus. At this the stage, the nuclear membrane has been dissolved, the chromosomes have become thicker. Centrosomes nucleate asters of microtubule that search for chromosomes to attach to. Other microtubules nucleated by the chromosomes will help to assemble the bipolar spindle. The chromosome centromeres where the kinetochores are assembled are an important attachment point for the microtubules. This attachment is controlled by the metaphase spindle checkpoint.

Metaphase: Being Under Surveillance. The chromosomes have reached their maximum condensation state. One pair of sister chromatids linked together by cohesins forms each chromosome. Each pair of chromatid kinetochores must have one kinetochore attached to microtubules nucleated by a centrosome and the opposite kinetochore attached to microtubules emanating from the opposite centrosome. During all this process, the spindle formation is controlled by the dynamic instability of the microtubules. At the end of metaphase, the spindle must be under tension with all the chromosome kinetochores attached to both centrosomes and aligned at the metaphase plate. Cell will remain in metaphase until all the above conditions are fulfilled leading to the spindle checkpoint switch off.

Anaphase: Chromosome Segregation. This stage is triggered once the cell has controlled the spindle under tension and all the kinetochores have been captured by microtubules. When the spindle seems the most stable, the cohesins that maintain the sister chromatids are degraded and each sister chromatid is pulled toward each centrosome forming two identical set of chromosomes.

Telophase: Get Ready for Cell Division. During anaphase while chromosomes are moving, many kinetochore proteins get detached from chromosomes to remain at the center of the cell where a central spindle is assembled. A contractile actin ring forms under the surface of the plasma membrane, around the central spindle. All these events lead to a contraction of the plasma membrane at the middle of the cell that will form two cells attached by the midbody.

Cytokinesis and Abscission: Daughter Cells Separation. This is the less understood event of mitosis: the two daughter cells must separate. To do so, the midbody must be broken and one of the cells will inherit a flemming body (remaining of the midbody). But more importantly, the cell must repair the plasma membrane to avoid leaking of cell contents. This is achieved by recruiting membrane vesicles from the previously dissolved Golgi. These vesicles also carry proteins required for cytokinesis. The very last step of cytokenesis called abscission is the physical separation of the two daughter cells.

Control of Mitosis by Phosphorylation. The protein kinases described here are all involved in the regulation of multiple events during mitotic progression. Analyzing the function of a mitotic kinase is not easy since knock down of the protein expression by RNA interference usually generates a phenotype that corresponds to the first event controlled by the enzyme. For instance, eliminating CDK1 leads to a cell cycle arrest in G2 phase. The cell does not enter mitosis because CDK1 is required for the G2/M transition. But CDK1 is also required for progression through mitosis. The function of each kinase is also tightly linked to their localizations during progression through mitosis, "being at the right place at the right time" (Fig. 2). One can for instance rescue Aurora B knock down by an Aurora A kinase chimera containing Aurora B localization sequences (17).

CDK1/Cyclin B Activity Delimits Mitosis. Cdk1/cyclin B activity appears in late G2 and peaks at metaphase (the middle of M phase) and is inactivated upon exit from mitosis by cyclin B destruction, degraded first on the spindle at the chromosome level together with cohesins (18). Cdk1 kinase plays important roles in early stages

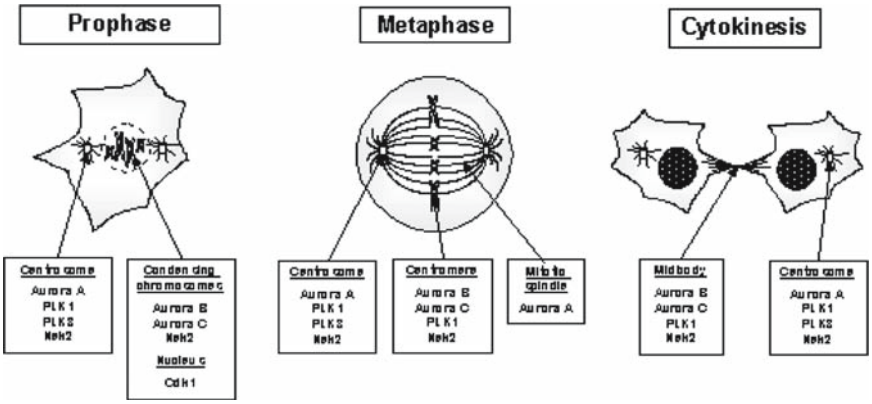

Fig. 2 Localization of the major mitotic kinase through the mitotic phase. One of the clues to succeed in mitosis for mitotic kinases is to be "at the right place at the right moment." The short summary of where the kinases have been found gives an idea of the complexity of the controls insured by mitotic protein kinases

that contribute to the G2/M transition. Cdk1 phosphorylates motor proteins involved in centrosomes separation required for bipolar spindle assembly (19). Cdk1 phosphorylates lamina inducing a destabilization of the nuclear structure leading to nuclear envelope breaks down (20). It also phosphorylates condensin contributing to chromosome condensation (21). When Cdk1 activity is maximum, it participates to the activation of the APC/C that insure the ubiquitination of the proteins targeted to be degraded at the metaphase/anaphase transition, including cyclin B and securin (22).

Plk1: A Very Busy Kinase. Plk1 kinase activity peaks in mitosis. The kinase is composed of a catalytic domain and a PBD (polo box domain) that must bind to a docking protein previously phosphorylated by a priming kinase to allow Plk1 activation (23). Also, Plk1 is activated by phosphorylation of its T-loop by an activated kinase (24). Plk1 localizes to the centrosomes, the kinetochores, and the midbody during mitosis. The kinase plays multiple roles during mitosis; it participates to the G2/M transition, its inhibition delays entry in mitosis. Among the Plk1 substrates one finds all the major players involved in the G2/M transition, CDC25, Myt1, and cyclin B1 (25–27). Plk1 would be involved in the feed back loop that controls the activation of Cdk1/cyclin B.

Plk1 activity is also required for centrosome maturation by recruiting protein necessary to nucleate the microtubules that will participate to bipolar spindle assembly; the kinase also interacts with and phosphorylates many proteins involved in microtubules dynamic (28, 29). In addition to be localized and active at the centrosome level, Plk1 also localizes to the chromosome kinetochores (30) where its activity participates to the localization of spindle checkpoint proteins. The exact function of Plk1 at the kinetochores and its participation to the spindle checkpoint remains to be clarified.

Plk1 is also required to activate the E3 Ubiquitine ligase APC/C required to trigger mitotic protein degradation. But although Plk1 directly phosphorylates APC/C subunits, the effect of this phosphorylation on APC/C activity is minor (31) compared with the phosphorylation by Cdk1/cyclin B1 (32). However, Plk1 contributes indirectly to APC/C activation by phosphorylating the APC/C-cdc20 inhibitor Emi1 in somatic cells. Phosphorylation of Emi1 by Plk1 triggers Emi1 degradation and APC/C-cdc20 activation (33, 34). This contributes to metaphase–anaphase transition controlled by APC/C-cdc20 and M/G1 transition controlled by APC/C-cdh1.

Finally evidence for a function of Plk1 in cytokinesis has been found in different organisms. Septum formation is impaired in the fission yeast kinase defective mutants, while ectopic septums are formed when the kinase is overexpressed (35, 36). In *Drosophila*, polo kinase mutant also shows cytokinesis defects at various stages of spermatogenesis (37). In vertebrate cells, the kinase localizes at the midbody (38). Plk1 also interact with and phophorylates kinesin proteins required in cytokinesis such as MKLP1 (39).

Aurora A: A Centrosome Protein. Aurora A is activated by binding to some of its substrates like TPX2, a mechanism that insures a local activation of the kinase (40). Aurora A is restricted to the centrosome area where it phosphorylates CDC25B contributing to G2/M transition (41). But unlike Cdk1, Aurora A is dispensable; its absence only delays entry into mitosis (42). Aurora A activity is required for centrosomes separation and maturation that consists in recruiting proteins involved in microtubule nucleation. The kinase phosphorylates motor proteins (43) and proteins required for astral microtubule nucleation (44). Aurora A might also be involved later in mitosis because its overexpression induced a bypass of the Taxol-induced mitotic checkpoint (45). The kinase is involved in cytokinesis since its overexpression induced polyploidy aggravated in the absence of p53 (46). However, these two last points need to be investigated further, in particular the relationship between Aurora A and p53. Upon exit from mitosis, Aurora A is degraded by the proteasome in a CDH1 dependant manner (47, 48).

Aurora B: A Chromosome Passenger Protein. Aurora B participates to at least two protein complexes with INCENP, and with INCENP/survivin/Borealin (49). Those proteins form the chromosome passenger protein family, they localize to the kinetochores until the metaphase–anaphase transition occurs then they relocalize to the midbody (50). Like Aurora A, Aurora B is activated by binding to some of its substrates. Aurora B clearly fulfills three distinct functions during mitosis. Aurora B is a histone kinase, it phosphorylates serines 10 and 28 on histone H3 and the serine 7 in the centromere histone variant CENP-A (51–53). The function of these phosphorylations is still debated: chromosome condensation? Loading of mitotic proteins on chromosome? Signaling mitosis?(54)

Aurora B also phosphorylates MCAK (mitotic centromere-associated kinesin) that results in the inactivation of its microtubule depolymerase catalytic activity and its targeting to the kinetochores. MCAK is involved in the spindle checkpoint by correcting the nonamphitelic attachments of microtubules to the kinetochores

(55). Aurora B RNA interference or inhibition mainly induces the formation of polyploid cells indicating that Aurora B activity is required for cytokinesis. And indeed, the kinase phosphorylates vimentin, the kinesin ZEN-4/MKLP1, and MgcRacGAP, a GTPase activating protein (GAP) all required for cytokinesis (56–58).

Aurora C: An Aurora B Substitute? Aurora C is expressed only in testis (59). However, overexpression of Aurora C has been observed in number of cancer cell lines and tumors (60, 61). Aurora C was first described as an anaphase centrosome protein (60). However, it turns out that Aurora C when overexpressed behaved just like Aurora A in interphase and like Aurora B in mitosis (62, 63). Aurora C like other Aurora is activated by some of its substrates, in particular by Aurora B substrate such as INCENP (63). Not only Aurora C mimics Aurora B in mitosis but also it rescues Aurora B depleted cells (63). Strikingly, nobody has yet localized the endogenous protein or analyzed whether the kinase is expressed in normal cells and what would be its function.

NIMA: A Kinase with Many Relatives. NIMA (never in mitosis A) is an *Aspergillus nidulans* protein kinase. Mutations that inactivate the kinase led to a late G2 arrest with cells harboring duplicated but unseparated centrosomes (64). Among the 13 mammalian Nek, Nek2 is the closest NIMA relatives, its activity is absolutely required for mitosis. Nek2 phosphorylates C-Nap1 (centrosomal Nek2-associated protein 1). Its phosphorylation is required for centrosome separation that is a prerequisite to bipolar spindle assembly (65). Nek2, at least in *Drosophila*, might also have a role late in mitosis since its overexpression leads to cytokinesis defects (16). These functions again are related to the localization of the kinase: the centrosomes and the kinetochores. Human cells express two isoforms of Nek2, Nek2A and Nek2B. Nek2A is degraded by the APC/C upon entry into mitosis whereas Nek2B remains stable during mitosis (15, 66). Nek2 is activated by trans-autophophorylation and inhibited by dephosphorylation by the phosphatase PP1 (67).

Other members of the Nek kinase family play roles during mitosis. Nek6 that is highly expressed during mitosis is required for mitosis progression because its inhibition provokes a metaphase arrest (68, 69). Nek9 that is a mitotic centrosome kinase phosphorylates and activates Nek6 (68). Inhibition of Nek9 impairs bipolar spindle assembly (70).

Mitotic Kinases and Cancer. In 1914, Boveri proposed aneuploidy (abnormal chromosome number) arising from mitotic defects as a mechanism that might lead to oncogenesis. Abnormal mitosis can indeed generate cells with multiple centrosomes and abnormal number of chromosomes frequently observed in cancer cells (71).

Boveri was right; chromosome instability and aneuploidy generate genetic defects that are hallmarks of tumorigenesis. They arise through defects during mitosis when chromosomes are unequally segregated between the two daughter cells. Neoplastic development is a multistep mechanism due to an accumulation of genetic defects that breaks the balance between growth-inhibitory signal and

division-promoting signal. Tumors then would derive from one cell in which the growth-inhibitory signal is down regulated (loss of tumor suppressor genes) and the division-promoting signal is elevated (gain of proto-oncogenes). One of the best examples is the transformation of human cell line achieved by coexpression of the SV40 large-T oncoprotein, the *H-ras* oncogene, and the telomerase catalytic subunit (72).

Chromosome segregation is a finely regulated process insured by the mitotic spindle that is a highly dynamic microtubule-based structure. The mitotic spindle is composed of two centrosomes connected by microtubules to the chromosomes aligned at the metaphase plate in the centre of the structure. In every pair of sister chromatid, each chromatid is connected to opposite centrosomes forming amphitelic attachment. During segregation, each sister chromatid migrates to one pole of the cell leading to the formation of two identical groups of chromosome. This bipolarity is necessary to form two daughter cells with the same DNA content during cytokinesis. In mammalian cells, each spindle pole is organized around a centrosome. Remarkably, in cancer cells, the number, the structure, and the function of centrosomes are often abnormal and correlate with aneuploidy and chromosome instability.

So, because the mitotic spindle plays a central role in chromosome segregation, many proteins involved in its establishment and in its regulation are often misregulated in cancers. This is the case for the mitotic protein kinases Cdk1, Aurora A, B, and C, Plk1, and Nek2 protein kinases (Table 1).

Table 1 An overview of relationship between mitotic kinase expression and cancer

Protein kinase	Expression in cancer	Cancers associated
Aurora A	Amplification of gene locus (20q13) Over-expression	Breast, colon, pancreatic, bladder & ovarian cancer, prostate cancer & neuroblastoma
Aurora B	Over-expression	Colorectal cancer, thyroid carcinoma, non-small cell lung carcinoma & prostate cancer
Aurora C	Over-expression	Thyroid carcinoma
Plk1	Over-expression	Non-small cell lung carcinoma, head and neck cancer, oesophageal and gastric cancer, breast, ovarian & endometrial cancer, colorectal cancer, thyroid cancer, glioma & melanoma
Plk3	Down-regulation	Head/neck squamous carcinoma, lung carcinoma & colon tumour
	Over-expression	Epithelial ovarian tumour
Nek2	Over-expression	Ewing's tumour, non-hodgkin lymphoma, breast, cervical and prostate carcinoma
	Amplification of gene locus (1q32)	Breast & gastric cancer
Cdk1	Over-expression	Colon adenoma, colorectal carcinoma and esophageal adenocarcinoma

CDKs. Alterations of Cdks have rarely been observed in cancer, and overexpression of Cdk1 and Cdk2 has been reported in colon adenomas (73, 74). However, alterations of proteins that regulate Cdks such as cyclins, Cdk-activating enzymes, and CKI are frequently observed (75, 76). For instance, cyclin A is overexpressed in lung carcinoma and elevated expression correlated with shorter survival (77). But the best proves that Cdk hyperactivities are involved in cancer is the fact that drugs inhibiting Cdks are particularly effective to inhibit tumor progression. A large variety of compounds are actually on the market and their successes are due to their effects, inhibition of cell proliferation, activation of apoptosis, and in some cases they can even trigger differentiation (78–80).

Aurora A. The gene encoding Aurora A is located on chromosome 20q13. This chromosome region is frequently found amplified in human cancers, and the amplification is associated with overexpression of the protein kinase (81). This Aurora A amplification/overexpression is detected in cancers like breast, colon, pancreatic, bladder, ovarian, prostate cancer, and neuroblastoma (82–85). Furthermore, the *Aurora A* gene copy number correlates with chromosomal instability and aneuploidy in human bladder tumor. Overexpression of the kinase also correlates with clinical aggressiveness of the tumor (84, 86). Aurora A has also been found mutated in several cancers, the mutation that is proposed to be due to polymorphism designs Aurora A as a candidate susceptibility gene (87).

In vitro Aurora A kinase overexpression induces aneuploidy and abnormal centrosome numbers leading to cell tumorigenic transformation (82, 83). Long-term overexpression of Aurora A is also sufficient to induce tumor formation in mice, after a long period of genomic instability (88). However, it is not clear how the kinase induces tumorigenesis, it has been proposed that Aurora A overexpression would be sufficient to escape negative regulation by tumor suppressor pathway. Aurora A kinase interacts with and phosphorylates the tumor suppressor protein p53. Phosphorylation of p53 induced its degradation through mdm2 (89) and reduced it transactivation activity (90). Because p53 plays a major role in carcinogenesis, its interaction with Aurora A might be important in the kinase oncogenic activity. Moreover, Aurora A kinase is a RasGap Src homology 3 domain binding protein and forms a complex with RasGap and Survivin proteins. This interaction inhibits Aurora A activity (91). Because RasGap is also a negative regulator of Ras pathway, it has been suggested that in cell overexpressing Ras, there would not be enough RasGap to inactivate both Ras and Aurora A leading to Aurora A hyperactivity participating to oncogenesis.

As mitosis regulators, the expression levels of the major mitotic kinases are crucial for cell division. In many cancers, up and down regulation of their expression have been observed, underlying the importance to follow the expression level of mitotic kinases for developing new targeted therapy.

Aurora B. Aurora B overexpression has been found in many cancers like colorectal cancer (92, 93) or thyroid carcinoma (94). In colorectal and prostate cancer, Aurora B overexpression increases in correlation with the tumor malignancy (92, 95). However, unlike Aurora A, *Aurora B* gene has never been found amplified and

the origin of Aurora B overexpression is actually unknown. Also unlike Aurora A, Aurora B is not an oncogene, but its overexpression induces metastasis. Aurora B overexpression results in hyperphosphorylation of histone H3 on serine 10 (96). This increase in serine10 phosphorylation is observed on lagging chromosomes during mitosis (96). Does hyperphosphorylation of histone H3 induce chromosome instability and aneuploidy? It seems so since, lagging chromosomes have been observed in cells transfected with a Ser10 phospho-mimetic form of histone H3 (96). Whether hyperphosphorylation of H3 participates to segregation defect is obvious, whether it participates to metastases apparition is not clear. Although Aurora B overexpression in cancer cells correlates with genetic instability (97), how Aurora B expression is linked to cancer remains to be determined. However, inhibition of Aurora kinases (especially with anti-Aurora B drugs) efficiently reduced tumor growth in mice (98).

Aurora C. Little is know about this third member of Aurora kinase family. In normal physiological conditions, Aurora C is expressed only in testis, (59). However, cancer cell lines expressed the kinase (60). Aurora C is highly expressed in human thyroid carcinoma cell lines and tissues, where its expression correlates with the aggressiveness of the tumor (61). Overexpression of Aurora C gives rise to polyploid cells. Like for the other Aurora kinases, the phenotype is aggravated in the absence of p53 (62). Because Aurora C is very close to Aurora B, one would expect overexpression of Aurora C to have the same consequences than over-expression of Aurora B.

Plk1. Overexpression of Plk1 in rodent cells is sufficient to confer a transform phenotype indicating that Plk1 is a potential oncogene (99). In agreement with this data, Plk1 has been found overexpressed in a large variety of cancers (100 for review). And high level of Plk1 is a sign of bad prognosis in several cancers (101–105). Beside overexpression, mutation in Plk1 has been observed in cancers; some of the mutations inhibit the interaction of Plk1 with Hsp90 and stabilize the kinase leading to a hyperactivity of Plk1 (106). Like for Aurora kinases, overexpression of Plk1 generates genomic instability by triggering the formation of polyploid cells (107) frequently observed in cancer cells (108). Taking together these data designed Plk1 as a good target for inhibitors used as anticancer drugs. And indeed inhibition of Plk1 was reported to have different effects in cancer cells vs. normal cells (28). Inhibition of Plk1 arrests tumor cells in culture as well as it reduces tumor growth in mice indicating that the kinase is absolutely required for cells that highly proliferate (109–110).

Nek2. Ewing's tumor cell line derived (a paediatric osteosarcoma) and non-Hodgkin lymphoma show elevated level of Nek2 mRNA, and the transcript level increase correlates with aggressiveness (111). Nek2 is also overexpressed in cervical and prostate carcinoma as well as in gastric and breast in which the chromosomal region 1q32 corresponding to the human *Nek2* gene locus is amplified (six times in breast cancer) (112, 113). Nek2 is not a proto-oncogene; however, its overexpression provokes defects in centrosome organization and function. In HBL100 cells, overexpression of human Nek2 induces the formation of aneuploid cells containing abnormal numbers of centrosomes a hallmark of cancer cells (71).

Conclusion

This short review only describes the most known mitotic protein kinases, we voluntarily omitted checkpoint kinases and others to make this review comprehensive for people that are not familiar with the protein kinase world. It is important to notice that many other mitotic protein kinases remain to be discovered and studied as demonstrated by recently performed screens in search for novel kinases (114).

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