AURORA KINASES AS THERAPEUTIC TARGETS OF ANTIONCOGENIC DRUGS VICTOR M. BOLANOS-GARCIA pdf

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Aurora kinases are serine/threonine kinases essential for the onset and progression of mitosis. Aurora members share a similar protein structure and kinase activity, but exhibit distinct cellular.

A Structural Perspective A. The human genome encodes for kinases that have a structurally conserved catalytic domain and includes about a dozen of cell division specific ones. Yet each kinase has unique structural features that allow their distinct substrate recognition and modes of regulation. These unique regulatory features determine their accurate spatio-temporal activation critical for correct progression through mitosis and are exploited for therapeutic purposes. In this review, we will discuss the principles of mitotic kinase activation and the structural determinants that underlie functional specificity. Introduction Protein phosphorylation is a key regulatory mechanism influencing various cellular processes such as cell growth, cell motility, cell differentiation and cell division. Most notably, protein phosphorylation peaks during mitosis and the timing coincides with the cell division-related chromosomal and cytoskeletal reorganization Dephoure et al. Consequently, mitotic protein kinases are considered central players orchestrating the mitotic progression and accurate spatio-temporal regulation of their activity becomes essential for error-free chromosome segregation. Many mitotic kinases are well characterized in terms of their structure and function. Though mitotic kinases share significant structural similarities, their cellular localization, enzymatic activity and substrate specificity are determined by diverse mechanisms. In this review, we will summarize our understanding of how structurally conserved and distinct features determine correct spatio-temporal regulation of kinase activity during mitosis. When the kinase is catalytically active, the C-helix packs against the N-terminal lobe Kobayashi et al. The ATP binding pocket is largely conserved across kinases and is surrounded by relatively less conserved pockets often exploited for inhibitor design Noble et al. The peptide backbone of the hinge region connecting the N- and C-terminal lobes makes hydrogen bonds to the adenine ring of the ATP, while nonpolar aliphatic residues lining the pocket interact with the purine structure. Note that when generating a kinase dead mutant, this lysine usually is targeted. Representative structures of mitotic kinases I. Key structural features are highlighted: C-helix light orange , hinge region involved in ATP binding blue , and activation segment cyan. The characteristic structural feature of an active enzyme, the salt bridge between a Lys and Glu from the N-terminal lobe and the C-helix is highlighted in stick representation. This activation segment is usually remodeled during kinase activation through phosphorylation, although intra- or inter-molecular protein binding can also trigger activation segment remodeling Bayliss et al. When non-phosphorylated, the activation segment is disordered and auto-inhibits the kinase by obstructing the substrate binding site. Phosphorylation of the activation segment on a phosphoacceptor serine or threonine typically activates the kinase by stabilizing the substrate-binding site. The negatively charged phosphate group is engaged by the basic residues contributed by the C-helix, the N-terminal lobe and the activation segment to stabilize the substrate-binding platform and hence the active conformation of the kinase Endicott et al. Pioneering studies in yeast, sea urchin and Xenopus showed that phosphorylation and cyclins controlled the activity of CDKs to drive the cell cycle. Cyclin levels are regulated throughout cell cycle both at the transcriptional and proteolytic level, which in turn activates CDK activity temporally Evans et al. Cyclins have a cyclin box domain that binds to the N-terminal lobe and the C-helix of the kinase domain Kobayashi et al. This mode of activation is broadly conserved in CDK1 Cdc2 and Cdc28 in budding and fission yeast respectively , which upon cyclin B binding initiates mitosis Santamaria et al. The Aurora family of kinases mainly Aurora A and Aurora B, are among the well characterized protein kinases Bayliss et al. These exhibit basal level of kinase activity on their own, but their full activation requires specific binding partners: Though the activation loop auto-phosphorylation is sufficient for basal activity, facilitating the right conformation of the loop is required for full activation, and is achieved by the binding of TPX2 and INCENP to Aurora A and Aurora B kinases, respectively Bayliss et al. A short N-terminal fragment of TPX2 binds between the N-lobe and activation loop of Aurora A and by doing so it stabilizes the activation loop in a fully active conformation. This makes the activation loop phosphorylation pT inaccessible for counteracting phosphatases and thus maintains the fully active state of Aurora A. Bub1 is a kinetochore-associated protein kinase which regulates the Spindle Assembly Checkpoint SAC and kinetochore-microtubule attachment Elowe, Structural characterization of Bub1 kinase domain reveals the role of its N-terminal extension in positioning the C-helix and stabilizing the conformation of the activation segment Lin et al. However, the activation segment conformation seen in the crystal structure does not appear to be suitable for substrate binding and activation loop phosphorylation has been implicated to enhance kinase activity and substrate recognition Lin et al. Representative structures of mitotic kinases II. Regulation by Phosphorylation Activation segment phosphorylation regulates kinase activity of several kinases during mitosis. Both Aurora A and Aurora B kinases undergo auto-phosphorylation within their activation segments T and T in Aurora A and Aurora B, respectively which is essential for their increased kinase activity Bayliss et al. Bub1 undergoes constitutive autophosphorylation in its activation loop throughout cell cycle, which is suggested to trigger reorganization in the substrate binding site and enhance kinase activity Lin et al. Likewise, Mps1 auto-phosphorylates multiple residues in its activation loop to activate itself Mattison et al. The crystal structure of Mps1 kinase dead mutant revealed that it adopts an inactive conformation Figure 2 , where the activation loop is disordered and displaces the C-helix Chu et al. Auto-phosphorylation of the activation loop may reorient and allow correct positioning of the C-helix for full activity. Phosphorylation within the kinase module has also been used to inactivate kinases. For example, the wee1 kinase inhibits CDK1 by phosphorylating the Tyrosine 15 in the N-terminal glycine-rich loop and obstructing access of the substrate to the kinase active site Russell and Nurse, ; Parker and Piwnica-Worms, ; McGowan and Russell, ; Welburn et al. This inhibition is reversed by the phosphatase Cdc25 Frazer and Young, However, the intrinsic activity of the haspin kinase is inhibited during prophase by its conserved basic N terminus haspin , human numbering preceding the kinase domain. During prophase to metaphase transition, the concerted activities of CDK1 and Plk1 relieve the auto-inhibition through phosphorylation in the N-terminal segment, and thus restrict the haspin activity to metaphase Ghenoiu et al. Mechanisms for Achieving Substrate Specificity Kinases achieve substrate specificity through multiple mechanisms in mitosis Ubersax and Ferrell, ; Johnson, In addition, specific subcellular localization of kinases also facilitates substrate specificity by spatially restricting the kinases. Consensus Phosphorylation Motifs Kinase substrate specificity is generally determined by the architecture of the substrate binding site, which might select negatively against certain residues flanking the phosphorylation site. The identification of substrates in vitro and in vivo thus far has helped define kinase substrate specificity. Typically about amino acids flanking the phospho-acceptor residue P can contribute to the selectivity of kinases for their substrate. As a result, other residues other than a proline at this position are unfavored. The identification of multiple budding yeast kinetochore Aurora B kinase substrates, allowed to define an Aurora consensus phosphorylation sequences Cheeseman et al. An integrated approach combining biochemical, proteomic and structural biology methods identified substrates of the Haspin kinase, its consensus substrate recognition motif and their mode of interaction Maiolica et al. However, kinases do tolerate variations in the consensus sequence of their substrates. Proteomic studies combined with known phosphorylation consensus sites and bioinformatics represent powerful ways to uncover and validate new substrates in vivo Dephoure et al. Quantitative proteomics also inform substrate specificity of kinases not previously known. For example, such studies revealed that Mps1 and Plk1 share the same substrate preference Dou et al. Overall the substrate consensus motif plays a determining role in kinase-substrate interactions. Substrate Priming Kinases may use docking sites or sites that are primed by another kinase to enhance their substrate selectivity. For example, to bind and to be phosphorylated by Plk1, a substrate generally needs to be primed by another kinase Lee et al. By doing so the PBD of Plk1 recruits the catalytic domain to the phosphorylated substrates Cheng et al. CDK-cyclins also use docking sites to recognize and phosphorylate temporally their substrates. Substrates that do not have this docking site are phosphorylated later during mitosis or may not be recognized by the CDK-cyclin complex Koivomagi et al. Overall the docking site interactions increase the local concentration of the substrate and ensure accurate spatio-temporal substrate phosphorylation essential for correct mitotic progression Brown et al. Subcellular Localization Many mitotic kinases rely on spatial targeting to phosphorylate their specific substrates. This restricts the activity of the kinase to generate gradients of kinase activity. The most well characterized spatially-targeted kinases are Aurora A and B kinases and they appear to share the same substrate specificity Fu et al. However Aurora A predominantly associates with centrosomes and mitotic spindle, while Aurora B is localized at centromeres and kinetochores. Due to their distinct subcellular localization, while Aurora B phosphorylates substrates such as histone H3, kinetochore proteins and spindle midzone proteins Gruneberg et al. The molecular basis for the recruitment of Mps1 kinase to the outer kinetochore is also well established. In addition, direct interaction of Mps1 with the Ndc80 complex is crucial for its localization and function Hiruma et al. While the N-terminal extension of Mps1 directly interacts with the CH-domain of Ndc80 adjacent to the microtubule binding region , the conserved middle region of Mps1 interacts with the Nuf2 CH domain. The affinity of Mps1 is higher for Aurora B-phosphorylated Ndc80, indicating that Aurora B promotes Mps1-Ndc80 interaction in response to unattached kinetochores Ji et al. Mps1 can then phosphorylate Knl1 to activate the spindle checkpoint. Summary High resolution mechanistic understanding of kinase regulation is essential not only to define how kinases achieve error-free cell division, but also to exploit the differences in their regulatory mechanisms to specifically target them in mitosis-related human disorders. Structural studies of kinases thus far have provided key insights into the similarities and differences in the modes of activation and regulation of many mitotic kinases. In this review, we summarize how key structural regulatory elements such as the relative orientation of the C-helix, activation segment conformation and spatial regulatory elements responsible for correct kinase sub-cellular localization achieve accurate kinase function. However, there are still many open questions, particularly on factors determining the graded level of kinase activation and its implications on their mitotic role. More structural analyses of kinases in complex with their regulatory binding partners with and without bound substrates, and their functional implications in cells will undoubtedly further advance our mechanistic understanding of this essential class of mitotic regulators. Author Contributions JW and AJ have made a substantial, direct and intellectual contribution to the work, and approved it for publication. Conflict of Interest Statement The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Acknowledgments We thank M. Spatial exclusivity combined with positive and negative selection of phosphorylation motifs is the basis for context-dependent mitotic signaling.

2: Aurora kinases_å›¾æ–‡_ç™¾åº¦æ–‡åº“

The study of protein kinases in human brain and in cell culture / FÃ©licien Karege [et al.] -- Oncogene proteins: targets for cancer immune-cell therapy / Hiroshi Fujiwara and Masaki Yasukawa - PI3K/Akt/mTOR signaling pathway: implications for human cancer / Xiaolin Wan and Lee J. Helman -- Modulation of tumor angiogenesis by.

These important regulators of mitosis are over-expressed in diverse solid tumors. One member of this family of serineâ€"threonine kinases, human Aurora A, has been proposed as a drugable target in pancreatic cancer. The recent determination of the three-dimensional structure of Aurora A has shown that Aurora kinases exhibit unique conformations around the activation loop region. This property has boosted the search and development of inhibitors of Aurora kinases, which might also function as novel antioncogenic agents. Aurora kinases; Cell division; Kinase inhibitors 1. Introduction Being cellular division one of the hallmarks of living organisms, is not surprising that this process is tightly regulated by a vast number of proteins. Among this network of regulatory proteins, Aurora kinases are of particular relevance as they play a crucial role in cellular division by controlling chromatids segregation. Defects in chromatids segregation cause genetic instability, a condition associated with tumorigenesis. Aurora B is a chromosome passenger involved in cytokinesis and chromosome architecture Adams et al. More recently, a novel human Aurora C splicing variant Aurora C-SV which encodes a amino-acid protein, has been cloned and characterized Yan et al. As shown in Table 1, Aurora kinases exhibit differential substrate af? Mammalian genomes uniquely encode for three Aurora kinases, Aurora A, Aurora B, and Aurora C, while for other metazoans, including the frog, fruit? The yeast genomes S. Indeed, phylogenetic trees suggest that all three vertebrate Auroras evolved from a single urochordate ancestor. The comparison of the crystal structure of human Aurora A against that predicted from the amino acid sequences of human Auroras B and C also supports the notion that vertebrate Auroras B and C are closely related paralogs Brown et al. Structure Human Auroras Aâ€"C are kinases of a size ranging from to amino acid residues that exhibit a relatively high sequence divergence between species. For example, the overall sequence identities between human and rodent proteins are: As shown in Fig. The PEST-like motif has been identi? The mutation of this motif, which is located at the N terminus, signi? It has also been established that the main phosphorylation site of mouse Aurora C is threonine , which is phosphorylated by protein kinase A. Aurora A degradation is dependent on hCdh1 in vivo, not on hCdc20 Taguchi et al. Aurora A undergoes cell cycle dependent regulation: The cell cannot function with a high level of Aurora kinase activity, as its over-expression in cultured cells produces a transformed phenotype. Instead, Aurora B undergoes degradation by V. Domain organisation of Aurora kinases Aâ€"C. As shown here, Aurora kinases present three domains: In addition to the kinase activity, this central domain also presents regulatory motifs, as the crystal structure of the Aurora A-TPX2 complex has shown. Certainly, the detailed study of Aurora C regulation constitutes an interesting area of research. Aurora A The maintenance of a functional balance between mitotic checkpoint proteins and Aurora A is essential for the proper progression through mitosis. Moreover, this kinase is a key regulatory component of the p53 pathway as its overexpression leads to increased p53 degradation, which facilitates oncogenic transformation Katayama et al. Aurora B Aurora B also plays an essential role in chromosome segregation and cytokinesis and its kinase activity is required for bipolar chromosome orientation and V. A Amino acid sequence alignement of the catalytic domain of human Aurora kinases Aâ€"C. The conserved residues described by Brown et al. These non-conserved residues are particularly attractive for designing speci? The residues lining the active site are shown in brown color; the three non-conserved residues L, T and R are shown in red. C The three-dimensional structure of human Aurora A complexed with the microtubule associated protein TPX2 shows that the latter induces a dramatic conformational change on Aurora A, which in turn forces this kinase to adopt a more compact conformation. Although Aurora B plays a major role in the kinetochore assembly pathway in mammalian cells, only one Aurora B target, centromere protein-A, has been identi? Aurora C Very little is known on the function and regulation of this kinase. Aurora C is expressed at a moderate level albeit about an order of magnitude lower than Aurora B in diploid human? In contrast, the level of Aurora C is elevated in several human cancer cell types. Competition binding assays and transfection experiments revealed that, compared with Auroras B, Auroras C has a lower binding af? It has also been shown that an Aurora C kinase-dead mutant induces multinucleation in a dose-dependent manner and that siRNA mediated silencing of both Auroras B and C give rise to multinucleated cells. Interestingly, Aurora C is able to rescue the Aurora B silenced multinucleation phenotype, demonstrating that Aurora C kinase function overlaps with and complements Aurora B kinase function in mitosis Sasai et al. Thus, Aurora C is a chromosomal passenger protein localizing? Possible medical applications Aurora A has been recognized as a good marker of tumor progression and prognosis. Therefore, the inhibition of its kinase activity could help to reduce tumor aggressiveness. Although the crystal structure of human Aurora A revealed that its catalytic domain exhibits a similar topology as that observed in many kinases, 3 out of 26 residues lining its ATP-binding active site are variant Fig. Moreover, the activation loop region and a? Certainly, the analysis of ATP-binding domains Fig. Several Aurora inhibitors have been synthesized to date: Based on this rationale framework for designing anti-tumor drugs, it is not exaggerated to af? Current Biology, 10, â€” Cancer Cell, 3, 51â€" Molecular Cell, 12, â€" Evolutionary relationships of Aurora kinases: Implications for model organism studies and the development of anti-cancer drugs. BMC Evolutionary Biology, 4, 39â€" The cellular geography of aurora kinases. Nature Reviews Molecular Cell Biology, 4, â€" EMBO Reports, 3, â€" Mutational analysis of the phosphorylation sites of the Aie1 Aurora-C kinase in vitro. DNA and Cell Biology, 21, 41â€" Tension between two kinetochores suf? 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Mammalian genomes uniquely encode for three Aurora kinases, Aurora A, Aurora B, and Aurora C, while for other metazoans, including the frog, fruitfly and nematode, only Aurora A and B kinases are known.

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