1. Phylogeny – Aurora kinase A (AURKA) is a member of the highly conserved Aurora kinase family, which in vertebrates comprises three paralogs: Aurora-A, Aurora-B, and Aurora-C. Phylogenetic analyses indicate that all vertebrate Aurora kinases evolved from a single ancestral gene closely related to the yeast Ipl1, with gene duplication events in early vertebrates leading to the distinct Aurora-A and Aurora-B/C lineages (brown2004evolutionaryrelationshipsof pages 2-3, willems2018thefunctionaldiversity pages 1-2). Among these, Aurora-A represents a single ortholog consistently found in mammals and cold-blooded vertebrates, while Aurora-B and Aurora-C share a more recent duplication event in mammals. In the human kinome, Aurora kinase A is assigned to the serine/threonine protein kinase group and is part of an evolutionarily conserved core of mitotic regulators whose origin can be traced to early eukaryotic ancestors (brown2004evolutionaryrelationshipsof pages 2-3, willems2018thefunctionaldiversity pages 2-4).
2. Reaction Catalyzed – Aurora kinase A catalyzes the transfer of the γ-phosphate from ATP to serine or threonine residues on protein substrates. The enzymatic reaction can be summarized as: ATP + [protein]–(L-serine or L-threonine) → ADP + [protein]–(L-serine/threonine)-phosphate + H⁺. This phosphorylation reaction is essential for the regulation of numerous substrates involved in mitotic progression (brown2004evolutionaryrelationshipsof pages 2-3, pflug2012proteinkinaseselectivity pages 21-25).
3. Cofactor Requirements – The catalytic activity of Aurora kinase A is dependent on ATP as the phosphate donor, and the binding of ATP at the cleft between its N-terminal and C-terminal lobes is stabilized by the presence of a divalent cation, typically Mg²⁺. Mg²⁺ is required to coordinate the phosphates of ATP, thereby facilitating the nucleophilic attack by the substrate hydroxyl group (attwood2021trendsinkinase pages 14-15, brown2004evolutionaryrelationshipsof pages 1-2).
4. Substrate Specificity – Aurora kinase A is a serine/threonine kinase whose substrate specificity is determined by its highly conserved catalytic domain as well as by local regulatory interactions. It phosphorylates numerous proteins that function in centrosome maturation, spindle assembly, and mitotic progression. Characterized substrates include ARHGEF2, BORA, BRCA1, CDC25B, DLGP5, HDAC6, KIF2A, LATS2, NDEL1, PARD3, PPP1R2, PLK1, RASSF1, TACC3, p53/TP53, and TPX2. Although a simple consensus motif has not been universally defined, substrate recognition is influenced by basic residues in the vicinity of the target serine/threonine and by binding interactions—such as those mediated by TPX2—which further refine substrate specificity (willems2018thefunctionaldiversity pages 13-14, brown2004evolutionaryrelationshipsof pages 2-3).
5. Structure – Aurora kinase A exhibits a canonical bilobed kinase fold common to serine/threonine protein kinases. Its structure is composed of an N-terminal lobe, which contains a five-stranded anti-parallel β-sheet along with a glycine-rich loop that contributes to nucleotide binding, and a predominantly α-helical C-terminal lobe that houses the activation loop and catalytic residues. The ATP-binding pocket is situated between these lobes, and key features include a conserved lysine residue in the β3 strand that forms a salt bridge with a glutamate in the αC helix, thereby maintaining an “αC-in” active conformation (attwood2021trendsinkinase pages 7-9). Unique to Aurora-A is the presence of three variant residues—Leu215, Thr217, and Arg220—lining the catalytic site, which distinguish it from other Aurora isoforms (brown2004evolutionaryrelationshipsof pages 5-7). In addition to the catalytic domain, Aurora-A contains an N-terminal A-box motif that is important for activation and a C-terminal destruction box (D-box) that mediates its regulated proteolysis during mitotic exit (brown2004evolutionaryrelationshipsof pages 5-7, lindon2016ubiquitinmediateddegradationof pages 7-8). High-resolution crystal structures of Aurora-A, including inhibitor-bound forms (e.g., with VX-680), have provided further insights into the conformational dynamics, activation loop phosphorylation, and inhibitor binding within the ATP-binding pocket (brown2004evolutionaryrelationshipsof pages 9-10, willems2018thefunctionaldiversity pages 14-15).
6. Regulation – The regulation of Aurora kinase A is mediated by complex post-translational modifications and protein–protein interactions. Autophosphorylation of the activation loop—most notably at Thr288—is crucial for attaining full kinase activity, a process often promoted by binding partners such as TPX2; TPX2 not only stabilizes the active conformation but also directs Aurora-A to mitotic spindles (willems2018thefunctionaldiversity pages 14-15, brown2004evolutionaryrelationshipsof pages 9-10). In addition, Aurora-A is subject to ubiquitin-mediated degradation, particularly during mitotic exit, which is orchestrated by the anaphase-promoting complex/cyclosome (APC/C) complex in collaboration with the coactivator Cdh1. Degradation signals are embedded within short linear motifs such as the A-box and D-box located in its N-terminal region; phosphorylation-dependent masking or unmasking of these degrons plays a key role in determining the timing of its proteolysis (lindon2016ubiquitinmediateddegradationof pages 2-3, lindon2016ubiquitinmediateddegradationof pages 3-5). Aurora-A is also modulated by additional post-translational modifications such as acetylation and interactions with other mitotic proteins, which further fine-tune its activity during cell cycle progression (lindon2016ubiquitinmediateddegradationof pages 5-7, willems2018thefunctionaldiversity pages 15-15).
7. Function – Aurora kinase A plays a central role in mitotic progression by orchestrating key events during cell division. It localizes predominantly to centrosomes and spindle microtubules, where it is essential for centrosome maturation, duplication, and separation; these functions are critical for the establishment of a bipolar spindle and for accurate chromosome alignment and segregation during mitosis (brown2004evolutionaryrelationshipsof pages 1-2, willems2018thefunctionaldiversity pages 4-5). Aurora-A is also required for the initial activation of cyclin-dependent kinase 1 (CDK1) at centrosomes, an indispensable step in the G2/M transition. Its substrates include several proteins that regulate spindle assembly checkpoint signaling and microtubule dynamics, thereby ensuring that mitosis proceeds with high fidelity. Furthermore, the aberrant overexpression or mutation of Aurora-A is implicated in chromosomal instability and tumorigenesis; its dysregulation is observed in a variety of cancers, including those of the breast and colon, which underscores its significance as both a prognostic marker and a potential therapeutic target (brown2004evolutionaryrelationshipsof pages 9-10, willems2018thefunctionaldiversity pages 16-17, moura2019phosphatasesinmitosis pages 39-41).
8. Other Comments – Several small-molecule inhibitors targeting Aurora kinase A have been developed with the aim of disrupting its catalytic activity, particularly as a strategy to counteract its oncogenic effects. Inhibitors such as VX-680, MLN8054, MLN8237 (also known as Alisertib), and other ATP-competitive compounds have been shown to impair mitotic progression and reduce tumor growth in various preclinical studies (brown2004evolutionaryrelationshipsof pages 7-8, attwood2021trendsinkinase pages 14-15, zheng2008chemicalregulationof pages 14-18). Due to its frequent overexpression and gene amplification in human cancers, Aurora-A is regarded as a high-priority target for novel anticancer therapies. In addition, mutations that affect regulatory motifs influencing protein degradation have been documented, and these alterations may contribute to the stabilization of Aurora-A in tumor cells. Such disease-associated mutations and the emerging resistance mechanisms to current inhibitors are driving ongoing research and clinical efforts to develop more selective and potent therapeutic agents (faisal2020developmentandtherapeutic pages 18-19, gani2015assessingproteinkinase pages 9-11).
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