## Phylogeny

• AURKC is a member of the Aurora kinase sub-family within the CMGC group of the human kinome, clustering most closely with its paralog AURKB and more distantly with AURKA (vats2025aurorakinasessignaling pages 1-2, moura2016rolesofhuman pages 57-60).  
• Orthologs are documented in Mus musculus, Rattus norvegicus, Danio rerio and Xenopus laevis, whereas a single ancestral Ipl1 fulfils the Aurora role in Drosophila melanogaster and Saccharomyces cerevisiae (willems2018thefunctionaldiversity pages 1-2, vats2025aurorakinasessignaling pages 1-2).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr ⇌ ADP + [protein]-O-phospho-Ser/Thr (unknownauthors2021disruptinginhibitorykappabkinase pages 45-48).

## Cofactor Requirements

Mg²⁺ or Mn²⁺ ions are required for catalytic turnover (azeez2019structuralmechanismof pages 5-6).

## Substrate Specificity

• Preferred consensus resembles that of AURKB: R/K/N-X-S/T-Φ, where Φ is a hydrophobic residue (azeez2019structuralmechanismof pages 1-2).  
Validated cellular substrates:  
 – Histone H3 S10 and S28 (azeez2019structuralmechanismof pages 8-9).  
 – INCENP S893/S894 (azeez2019structuralmechanismof pages 2-3).  
 – BIRC5/Survivin (sarı2024aurorakinasestheir pages 12-12).  
 – TACC1 S228 (sarı2024aurorakinasestheir pages 5-6).

## Structure

• Domain organisation: N-terminal segment (~1-38 aa), bilobal catalytic domain (39-290 aa) and short C-terminal tail containing an RxxL D-box (291-306 aa) (vats2025aurorakinasessignaling pages 2-4).  
• Crystal structures of fully active human AURKC bound to phosphorylated INCENP (PDB 6GR8, 6GR9; 1.75 Å) show an ordered activation loop with pThr198 anchored by Arg165 (HRD), Arg196 (activation loop) and Arg90 (αC helix) (azeez2019structuralmechanismof pages 2-3).  
• The INCENP TSSxxW motif embraces both faces of the αC helix; Trp897 stacks against His97 and His190, completing the regulatory spine and locking the kinase in the DFG-in active state (azeez2019structuralmechanismof pages 3-4).  
• Absence of Met249 precludes the domain-swap dimer observed for AURKB, favouring a monomeric configuration (azeez2019structuralmechanismof pages 3-4).

## Regulation

Post-translational modifications  
• Autophosphorylation at Thr198 is essential for catalytic activity (azeez2019structuralmechanismof pages 1-2).  
• CPC-dependent activation: phosphorylation of INCENP S893/S894 stabilises the activation loop and increases k\_cat; alanine substitution at either site raises K\_M and lowers catalytic efficiency (azeez2019structuralmechanismof pages 2-3).  
• PLK1 controls CPC localisation and thus AURKC spatial activation during cell division (santos2011arolefor pages 2-2).  
• Methylation of INCENP Arg887 diminishes binding affinity and down-regulates kinase activity (azeez2019structuralmechanismof pages 8-9).  
• Proteolysis: AURKC contains an internal RxxL D-box but lacks KEN and DAD/A motifs; this architecture suggests APC/C-mediated, Cdh1-dependent degradation distinct from AURKA/B (vats2025aurorakinasessignaling pages 2-4, lindon2016ubiquitinmediateddegradationof pages 5-7).  
Allosteric regulation  
• Binding of phosphorylated INCENP reorganises the αC helix and hydrophobic spine, fully activating the kinase (azeez2019structuralmechanismof pages 3-4).

## Function

• Highest expression in testis germ cells; low basal levels in placenta, lung, bladder and skeletal muscle (sarı2024aurorakinasestheir pages 2-3).  
• Serves as the catalytic core of the Chromosomal Passenger Complex with INCENP, BIRC5 and CDCA8, governing chromosome alignment, kinetochore-microtubule attachment, spindle-assembly checkpoint and cytokinesis in mitosis and meiosis (unknownauthors2021disruptinginhibitorykappabkinase pages 50-53, goldenson2015theaurorakinases pages 1-2).  
• Redundant with AURKB; can substitute for AURKB loss in mitotic cells (goldenson2015theaurorakinases pages 1-2).  
• Downstream phosphorylation of histone H3 (chromatin condensation) and TACC1 (spindle stability) links AURKC activity to faithful chromosome segregation (sarı2024aurorakinasestheir pages 5-6, azeez2019structuralmechanismof pages 8-9).

## Inhibitors

• VX-680 (Tozasertib): IC₅₀ = 4.6 nM for AURKC; co-crystal structure shows ATP-site binding that partially disrupts INCENP contacts (kovacs2023aurorabinhibitors pages 4-6, azeez2019structuralmechanismof pages 6-7).  
• BRD-7880: nanomolar affinity for Aurora B/C; binds hinge region while preserving INCENP interface, maintaining the active conformation (azeez2019structuralmechanismof pages 7-8).  
• CCT137690: IC₅₀ = 19 nM for AURKC (kovacs2023aurorabinhibitors pages 12-14).

## Other Comments

• Germline mutations Y248*, W279* and c.T1093C cause macrozoospermia with large-headed polyploid sperm and male infertility (sarı2024aurorakinasestheir pages 3-5, santos2011arolefor pages 6-7, moraes2024aurorakinaseas pages 9-9).  
• Aberrant over-expression is detected in several epithelial cancers, implying oncogenic potential (sarı2024aurorakinasestheir pages 5-6).

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