1. Phylogeny  
   Aurora kinase C (AURKC), also known as Aurora 3, AIE2, ARK3, STK13, is a member of the aurora kinase family, which in mammals includes Aurora A, Aurora B, and Aurora C. Phylogenetic analyses reveal that AURKC appears as a distinct paralog that arose by a gene duplication event from an ancestral Aurora B–related kinase; hence, while non‐mammalian vertebrates typically express only two aurora kinases (Aurora A and Aurora B), mammals uniquely express AURKC with a restricted expression pattern. AURKC clusters most closely with Aurora B based on sequence conservation and structural features, and its orthologs are found only in placental mammals. This evolutionary relationship places AURKC within the serine/threonine kinase core of the kinome that originated in early eukaryotes, with subsequent divergence and specialization in the mammalian lineage (brown2004evolutionaryrelationshipsof pages 5-7, willems2018thefunctionaldiversity pages 1-2, sarı2024aurorakinasestheir pages 1-2).
2. Reaction Catalyzed  
   Aurora kinase C catalyzes the transfer of a phosphate group from ATP to the hydroxyl group of serine or threonine residues on substrate proteins. The chemical reaction can be represented as: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (ke2003functionandregulation pages 1-4).
3. Cofactor Requirements  
   The catalytic activity of AURKC depends on divalent cations, with Mg²⁺ being required to facilitate proper ATP binding and phosphate transfer within its active site, a common feature among serine/threonine kinases (berlin…2010aurorakinaseinhibitorsrising pages 1-2, ke2003functionandregulation pages 1-4).
4. Substrate Specificity  
   AURKC displays substrate specificity that is central to its role as a component of the chromosomal passenger complex (CPC). It phosphorylates histone H3 on Ser-10 and Ser-28, modifications that are essential for chromosome condensation and segregation during cell division. In addition, AURKC phosphorylates key CPC subunits such as INCENP and BIRC5/survivin, which in turn enhance its catalytic activity, and it also targets TACC1 at Ser-228, thereby contributing to the stabilization of microtubule dynamics during mitosis and meiosis (balboula2014selectivedisruptionof pages 1-2, quartuccio2015functionsofaurora pages 1-2, quartuccio2015functionsofaurora pages 5-6).
5. Structure  
   AURKC contains a conserved catalytic (kinase) domain of approximately 250–300 amino acids that is characteristic of the aurora kinase family. This domain adopts the classical bilobal architecture consisting of a smaller, β-stranded N-terminal lobe and a larger, predominantly α-helical C-terminal lobe connected by a hinge region that positions the ATP molecule for catalysis. The kinase domain harbors critical regulatory motifs, including the DFG motif and an activation loop that contains a conserved threonine (Thr195), whose autophosphorylation is required for full catalytic activity. Flanking the conserved catalytic core, AURKC possesses an N-terminal regulatory region that is less conserved than in its paralogs; it lacks certain regulatory motifs (for example, a canonical KEN-box found in Aurora B) but may contain alternative degradation signals such as multiple D-boxes, contributing to its increased stability during meiotic divisions. Although high-resolution crystallographic data specific to AURKC have not been extensively reported, homology modelling and comparisons with Aurora B suggest a similar overall three-dimensional fold with key catalytic and regulatory features conserved across the family (kollareddy2008aurorakinasesstructure pages 1-2, quartuccio2015functionsofaurora pages 1-2, tang2017aurorakinasesnovel pages 12-13, willems2018thefunctionaldiversity pages 2-4).
6. Regulation  
   The kinase activity of AURKC is primarily regulated through autophosphorylation at a critical threonine residue within its activation loop (Thr195), an event that is essential for its full activation. Association with the chromosomal passenger complex, and in particular binding to the inner centromere protein (INCENP), further augments its activity by promoting a positive feedback loop in which phosphorylation of INCENP enhances AURKC catalytic function. In contrast to Aurora B, AURKC lacks a canonical KEN-box in its amino terminus, a feature that contributes to its increased protein stability during meiosis and allows sustained activity throughout the meiotic divisions in gametes. Additional post-translational modifications, including further phosphorylation events, likely contribute to the temporal and spatial regulation of AURKC during cell division, ensuring that its activity is confined to processes such as chromosome alignment and cytokinesis (tang2017aurorakinasesnovel pages 12-13, sasai2016auroracinteractionswith pages 19-20, balboula2014selectivedisruptionof pages 1-2).
7. Function  
   AURKC functions as a serine/threonine protein kinase that plays an essential role in regulating both mitosis and meiosis as a core component of the chromosomal passenger complex (CPC). In mitotic cells, AURKC contributes to the stabilization of kinetochore-microtubule attachments, correct chromosome alignment, and accurate chromosome segregation. It exerts part of its function by phosphorylating histone H3 on Ser-10 and Ser-28, events that are critical for chromatin condensation and progression through mitosis. In addition, AURKC phosphorylates CPC components such as INCENP and survivin, thereby modulating the proper function of this complex during cytokinesis. In the context of meiosis, AURKC is predominantly expressed in germ cells—for example, in spermatogenesis—and is crucial for orchestrating the unique chromosomal dynamics required for the production of haploid gametes; indeed, mutations in AURKC have been implicated in male infertility due to conditions such as macrozoospermia. Notably, AURKC can functionally compensate for the loss of Aurora B in certain cellular contexts, underscoring a degree of functional redundancy that is important for maintaining genomic stability during cell division (balboula2014selectivedisruptionof pages 1-2, quartuccio2015functionsofaurora pages 1-2, carmena2003thecellulargeography pages 1-2, lukasiewicz2009auroraacentrosome pages 7-8).
8. Other Comments  
   Several small-molecule inhibitors developed for aurora kinases inhibit AURKC along with AURKA and AURKB. For instance, compounds such as PHA-680632 and PHA-739358 have been shown to inhibit AURKC activity in the low nanomolar range, indicating their potential application in both research settings and cancer therapeutics. Despite its predominant expression in meiotically active germ cells, aberrant AURKC expression has been reported in certain cancer cell lines, and its overexpression may contribute to mitotic errors such as centrosome amplification and multinucleation. These observations, combined with its capacity to rescue Aurora B deficiency, underscore the importance of ongoing studies aimed at further delineating the molecular regulation and clinical relevance of AURKC. In addition, inherited mutations in AURKC are associated with male infertility, highlighting its physiological significance in spermatogenesis and emphasizing the need for further investigation into selective therapeutic targeting (berlin…2010aurorakinaseinhibitorsrising pages 7-8, goldenson2015theaurorakinases pages 1-3, du2021targetingaurkain pages 1-3, lukasiewicz2009auroraacentrosome pages 7-8).
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