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Molecules in focus

Aurora kinases

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Abstract

Aurora kinases A (also known as Aurora, Aurora-2, AIK, AIR-1, AIRK1, AYK1, BTAK, Eg2, MmIAK1 and STK15), Aurora B (also known as Aurora-1, AIM-1, AIK2, AIR-2, AIRK-2, ARK2, IAL-1 and STK12) and Aurora C (also known as AIK3) participate in several biological processes, including cytokinesis and dysregulated chromosome segregation. These important regulators of mitosis are over-expressed in diverse solid tumors. One member of this family of serine–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.
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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 A gene is located within the chromosome locus 20q13, which is a locus frequently detected in human breast tumors (Lengauer, Kinzler, & Vogelstein, 1998). Aurora B is a chromosome passenger involved in cytokinesis and chromosome architecture (Adams et al., 2000), while Aurora C expression plays a role in spermatogenesis at the time when cells assemble the two meiotic spindles and also cooperates with Aurora B to regulate mitotic chromosome dynamics in mammalian cells (Hu, Chuang, Lee, Tseng, & Tang, 2000; Sasai et al., 2004). More recently, a novel human Aurora C splicing variant (Aurora C-SV) which encodes a 290-amino-acid protein, has been cloned and characterized (Yan et al., 2005). As shown in Table 1, Aurora kinases exhibit differential substrate affinity, localization and elicit a different cell response.

Mammalian genomes uniquely encode for three Aurora kinases, Aurora A, Aurora B, and Aurora C, while for other metazoans, including the frog, fruitfly and

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Table 1
Human Aurora kinases A–C exhibit differential substrate affinity, subcell localization and associated activities

	Substrate	Cell localization	Effect of substrates-Aurora interaction
Aurora A	PP1, p53, Cdh-1, TPX-2, RasGAP, Ajuba	Mitotic spindle; centrosome	Spindle assembly; cytokinesis; centrosome maturation and separation
Aurora B	Histone H3; INCENP; CENP-A; desmin; Rec-8; vimentin; MCAK; survivin	Centrosome; central spindles; chromosome arms	Chromosome alignment and segregation; cytokinesis; microtubule dynamics
Aurora C	Aurora B; INCENP	Central spindles; chromosome arms?	Role in spermatogenesis; possible role in regulation of chromosome segregation and cytokinesis

nematode, only Aurora A and B kinases are known. The yeast genomes *S. cerevisiae* and *S. pombe* encode for only one Aurora-like homolog, suggesting that the functions of auroras have diverged throughout evolution. Indeed, phylogenetic trees suggest that all three vertebrate Auroras evolved from a single urochordate ancestor. Aurora A is an orthologous lineage in cold-blooded vertebrates and mammals, while structurally similar Auroras B and C evolved more recently in mammals from a duplication of an ancestral Aurora B/C gene found in cold-blooded vertebrates (Brown, Koretke, Birkeland, Sanseau, & Patrick, 2004).

2. Structure

Human Auroras A–C are kinases of a size ranging from 309 to 403 amino acid residues that exhibit a relatively high sequence divergence between species. For example, the overall sequence identities between human and rodent proteins are: Aurora A (82%), Aurora B (84%) and Aurora C (78%). As shown in Fig. 1, Aurora kinases A–C present a similar domain organization: a N-terminal domain of 39–129 residues in length, a protein kinase domain and a short C-terminal domain of 15–20 residues. The N-terminal domain of Auroras A–C shares low sequence conservation, which determines selectivity during protein–protein interactions (Carmena & Earnshaw, 2003). As shown in Fig. 2A for the human counterpart, the catalytic domain of Aurora kinases A–C is more conserved. The PEST-like motif has been identified in Aurora C. The mutation of this motif, which is located at the N terminus, significantly abrogates Aurora C kinase activity (Chen & Tang, 2002). It has also been established that the main phosphorylation site of mouse Aurora C is threonine 171, which is phosphorylated by protein kinase A. The alignment of Auroras A and B allows the identification of one distantly conserved 'KEN' motif, spanning 11–18 residues. The 'KEN' motif acts as a Cdh1-dependant anaphase-promoting complex (APC) recognition signal. The C-terminal domain of human Aurora B shares 53% and 73% sequence similarity to human Auroras A and C, respectively. 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., 2004).

3. Synthesis and degradation

Human Aurora A is turned over through the anaphase promoting complex/cyclosome (APC/C)-ubiquitin-proteasome pathway (Walter, Seghezzi, Korver, Sheung, & Lees, 2000). Aurora A degradation is dependent on hCdh1 in vivo, not on hCdc20 (Taguchi et al., 2002) and involves two different degradation motifs. The first corresponds to a N-terminal, D-Box-activating motif (RxLxPS). This motif confers functionality to a second motif, a D-Box, consisting of the sequence RxxLxxG. As shown in Fig. 1, the D-box is located at the C-terminus of the kinase domain and is the target of Fizzy-related proteins (Castro et al., 2002).

Aurora A undergoes cell cycle dependent regulation: it is inactivated or degraded when the cell proceeds in G_1 phase and its maximal expression occurs in G2/M phases. The cell cannot function with a high level of Aurora kinase activity, as its over-expression in cultured cells produces a transformed phenotype.

Although Aurora B possesses the same D-Box as Aurora A, it is not degraded by the same ubiquitin ligase. Instead, Aurora B undergoes degradation by

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