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Aurora kinase inhibitors

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Contents

Abstract

Most human cancer cells are characterized by changes in the amount or organization of DNA resulting in chromosome instability and aneuploidy. Several mitotic kinases, Aurora kinases amongst others, regulate the progression of the cell through mitosis. So far three Aurora kinases have been identified in man: Aurora-A, Aurora-B and Aurora-C. Aurora kinases were recently identified as a potential target in anticancer therapy, and various Aurora-A and Aurora-B kinase inhibitors are in development. In this review we provide a brief insight into the mechanism of action as far as currently available. We review the available pre-clinical data, discuss the clinical phase I data and try to give a direction for future headings.

Keywords: Aurora kinase; Aurora kinase inhibitor; Aurora-A; Aurora-B; Aurora-C; Pre-clinical; Phase I

1. Introduction

In normal cells mitosis is strictly regulated to maintain a diploid chromosome content. In contrast most cancer cells are characterized by changes in the amount or organization

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of DNA due to errors in mitosis resulting in chromosome instability and aneuploidy [1]. In fact, two characteristics of most cancer cells are (1) the loss of control of important regulatory cell cycle checkpoints and (2) a change in the organization or the amount of DNA compared with normal cells. Changes in DNA amount are mostly due to gains or losses of chromosomes as a result of incorrect segregation of chromosomes during mitosis. The segregation of the chromosomes is a complex process and involves the formation of a bipolar mitotic spindle guiding proper chromosome segregation. Considering the complexity of mitosis multiple checkpoint systems have been identified that ensure proper coordination. Progression through mitosis depends on three regulatory mechanisms: protein localization, proteolysis and phosphorylation performed by several serine/threonine kinases, known as mitotic kinases [2,3]. Several mitotic kinases are known to date including the Aurora kinases [2]. They are frequently overexpressed in human tumors and were identified as a potential new mitotic target in cancer therapy.

The original Aurora kinase was identified during a phenotypic screen for defects in mitotic spindles in *Drosophila* mutants. Aurora mutants were so named because of the morphological defects at the mitotic spindle resembling the Aurora borealis, or the Northern light [4]. The structure of the Auroras has been conserved through eukaryotic evolution. In man three members have been identified so far: Aurora-A, Aurora-B and Aurora-C. They possess an evolutionary conserved catalytic and N-terminal domain that varies in sequence and in length [2]. Aurora-A and Aurora-B have specific functions in mitosis including the regulation of centrosome duplication, bipolar spindle formation, alignment of chromosomes on the mitotic spindle and monitoring of the mitotic checkpoint. Aurora-A and Aurora-B are expressed in most normal cells, although their localization and the timing of activation during the cell cycle differ. Until recently Aurora-C expression was thought to be restricted to the testis, where it plays a role in meiosis [2]. However, recent investigations indicate that Aurora-C, like Aurora-B, is a chromosomal passenger protein with overlapping and complementing function to Aurora-B in mitosis [5].

2. Aurora-A

The Aurora-A gene lays within a region of chromosome 20q13, that is amplified in many epithelial malignant tumors, including breast, gastric, colon, ovarian and pancreatic cancers. Furthermore, overexpression of an active mutant of Aurora-A in *rat1* cells induced neoplastic transformation, indicating that Aurora-A is an oncogene. However, in a recent report controlled overexpression of Aurora-A in mice yielded only mitotic defects and mammary hyperplasia, but no malignant transformation [6] indicating that additional changes are needed to complete the neoplastic transformation of the cell. Overexpression of Aurora-A and centrosome amplification are early events in tumorigenesis in a rat mammary carcinogenesis model [7]. Furthermore, Aurora-A was shown to be a low-penetrance skin tumor-susceptibility gene, with an allelic variant (Ile31), whose presence was correlated with human colon tumor cells [8]. The amplification of the Aurora-A gene is also associated with the CIN (chromosomal instability) phenotype in colorectal cancers [9]. In pancreatic cancer polymorphisms in the Aurora-A genotype, with or without polymorphisms in the p16 genotype are associated with an earlier age at diagnosis [10]. These results support the hypothesis that Aurora-A amplification and overexpression help create the necessary genetic alterations required for tumorigenesis [11]. Additional changes like p53 inactivation or expression of pro-survival proteins are needed to complete the neoplastic transformation.

The oncogenic potential of Aurora-A probably results from two distinct functions of the kinase; (1) chromosome segregation as well as control of genomic stability and (2) regulation of entry into mitosis [11]. From the end of S phase to the beginning of the subsequent G1 phase Aurora-A is localized on duplicated centrosomes and during mitosis it is localized at the poles of the mitotic spindle. Its main function is assistance in the maturation of duplicated centrosomes by recruitment of multiple proteins and participation in spindle assembly and stability. By binding to its substrate, Aurora-A is activated by autophosphorylation [2]. The Aurora-A substrate conglomerate prevents Aurora-A from being dephosphorylated by a type I phosphatase that associates with the kinase [12]. The best studied Aurora-A substrate is TPX2. Other substrates include Ajuba, Eg5, CDC25B, p53 and BRCA-1 [2]. While TPX2 transports Aurora-A and causes its activation at the spindle poles, Ajuba activates the kinase during G2 phase.

The carefully orchestrated balance between Aurora-A kinase and its activator substrates and inhibitors is extremely important for normal mitosis. Therefore increase as well as decrease of Aurora-A kinase activity can cause errors of mitosis. Regression of Aurora-A expression by RNA interference (RNAi) delays mitotic entry in human cells [13] whereas overexpression of the wild-type kinase compromises G2 and spindle checkpoint function [14] as well as inhibits cytokinesis [15]. Aurora-A overexpression can be the result of amplification of genes, induction of gene transcription or post-translational stabilization [6]. In recent years parallels have been noticed between phenotypes associated with Aurora-A kinase overexpression and those caused by p53 loss of function [15]. Since then Aurora-A has been shown to phosphorylate Ser315 of p53, leading to its destabilization, mediated by Mdm2 [16]. Aurora-A RNAi caused dephosphorylation of Ser315, leading to p53 stabilization and concurrent G2/M cell cycle arrest. In addition, p53 itself has been shown to inhibit Aurora-A, an effect overcome by TPX2, the most intensively studied Aurora-A substrate [17].

Aurora-A overexpression is also related to the activation of NF-κB, a potent anti-apoptotic effector that may play a role in preventing apoptosis in cancer cells [18].