

Editorial

Relationship between Aurora Kinase C and Cancer

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INTRODUCTION

Aurora C is a meiotic chromosome passenger protein that is localized to duplicated centrosomes in G₂ phase, like Aurora A, and behaves like Aurora B during cell division. Inhibition of Aurora-C kinase activity induces abnormal kinetochore-microtubule attachment, premature chromosome separation, and cytokinesis failure in meiosis-I, which results in polyploid oocytes at the end of meiosis. These findings may explain, at least in part, how homozygous mutation in the Aurora-C gene causes polyploid spermatozoa in humans.

Over expression of Aurora-C in cancerous tissues and cell lines also raises questions about its potential role in carcinogenesis and its effect on the proliferative capacity of tumour cells. The expression levels of Aurora-C, Aurora-B and Aurora-B splice variants are commonly altered in tumour cell lines and tissues. These alterations in expression have been associated with tumourigenesis, tumour metastasis and tumour aggression.

Aurora Kinase C and Abnormal Mitosis

Aurora kinase C in its active form leads to abnormal centrosome number (more than 2 centrosomes per cell) when overexpressed in somatic cells, the hallmark of all cancer cells. This property of Aurora kinase C is related to its localization as the kinase is localized to duplicated centrosomes during G₂ phase, like Aurora kinase A. Hence it is very much debatable whether the oncogenic property of Aurora kinase C is due to its localization on centrosomes or due to some other unknown reasons as the kinase behaves like Aurora kinase A during interphase and behaves like Aurora kinase B during division phase. In this regard, Aurora kinase A is oncogene that is localized on centrosomes throughout the cell cycle but Aurora kinase B is not an oncogene but can augment Ras mediated transformation. So, like Aurora kinase A, Aurora kinase C is also an oncogene.

More over, like abnormal centrosome number, Aurora kinase C also leads to multinucleation (more than 1 nucleus/cell when the kinase is overexpressed in somatic cells. All multinucleated cells exhibited centrosome amplification. This multinucleation is due to mitosis with failure of the cytokinesis rather than endomitosis (mitosis without efficient anaphase) that would have given rise to 4N nuclei. Besides, aberrant mitotic structures such as lagging chromosomes and DNA strands between dividing cells in cells overexpressing active Aurora kinase C have also been found.

Aurora Kinase C and Mitotic Defects

The active overexpressed forms of Aurora kinase C leads to abnormal mitosis when the cells overexpressing the said kinase are injected into nude mice for tumour formation. Mitotic defects such as abnormal prometaphase and metaphase, lagging chromosomes in anaphase and abnormal telophase cells with cytoplasmic bridges have frequently been found in the tumour induced by Aurora kinase C. Thus the histological analysis of these tumours also confirms high proliferation rate of active Aurora kinase C.

Aurora Kinase C and Infertility

Aurora kinase C has been found in meiotically dividing spermatocytes and oocytes, implying a meiotic chromosome passenger protein in mammals. In mouse oocytes, Aurora C is a unique chromosomal passenger protein that regulates chromosome segregation, kinetochore-microtubule attachment and cytokinesis.

It has been found that a homozygous mutation (c.144delC) in the human Aurora C gene led to the production of large-headed multiflagellar polyploid spermatozoa and resulted in azospermia, and the same mutation also caused meiosis-I arrest in male spermatocytes. However, the molecular basis of how the Aurora C gene defect causes this phenotype is unclear. Another point mutation in exon6, C686 G→A causes almost azospermia with few detectable spermatozoa. Similarly, mutation in exon 3, Ile79 Val causes male infertility by impairing spermatogenesis.

Apart from infertility, Aurora C mutated men do not show any other health problems. Hence, this also proves Aurora kinase C to be a key regulator of cell cycle progression.

Aurora Kinase C and Cancer

Aurora kinase C in its active form leads to abnormal centrosome amplification (>2 centrosomes/cell) and multinucleation (>1 nucleus/cell) when overexpressed in somatic cells, found in all types of cancer cells. The kinase dead mutant type of Aurora kinase C in Human U2OS and HeLa cells also leads to abnormal number and multinucleation, but not in mouse NIH3T3 cells, showing the differential regulatory mechanism of Aurora kinase C gene in different cells.

Depending upon its kinase activity, Aurora kinase C induces *in vitro* transformation of mouse NIH3T3 cells when overexpressed. The kinase also shows *in vivo* oncogenic activity and induces tumour formation when injected into nude mice. More interestingly, such tumours show abnormal mitosis, like abnormal metaphase, lagging chromosomes and cytokinesis defects. It has been shown that inhibition of Aurora kinase C kinase activity induces abnormal kinetochore-microtubule attachment, premature chromosome separation, and cytokinesis failure in meiosis-I, which results in polyploid oocytes at the end of meiosis. These findings may explain, at least in part, how homozygous mutation in the Aurora kinase C gene causes polyploid spermatozoa in human.

Aurora kinase C behaves like a chromosome passenger protein during mitosis when it is overexpressed. Aurora kinase C can disrupt Aurora kinase B interaction with INCENP leading to a delocalization of Aurora kinase B. Aurora kinase C directly competes with Aurora kinase B not only for binding to INCENP it also competes for binding to survivin. This clearly demonstrates that overexpressed Aurora kinase C kinase behaves like a dominant negative kinase for Aurora kinase B leading to a cytokinesis defect. Aurora kinase C disrupts the chromosome passenger protein complexes necessary for cytokinesis. What about an effect on Aurora-A? Considering that in interphase Aurora kinase C localizes to centrosome together with Aurora kinase A one might also expect a dominant negative effect on Aurora kinase A as well. Remarkably the phenotype induced by Aurora kinase C overexpression is aggravated in the absence of active p53. This is also the case for Aurora kinase A and Aurora kinase B overexpression. In the presence of active p53 cells containing abnormal DNA content or abnormal centrosome number as a result of a mitotic defect might be eliminated during the G₁ phase by the p53-dependent checkpoint. Studies have demonstrated that a correlation exists between abnormal centrosome number and chromosomal instability in cancer. These defects that seem to appear in the earliest stages of cancer

development have been found in almost all types of cancer cells. For instance centrosome abnormalities are frequently observed in breast cancer cells, colorectal cancer cells and pancreatic cancer cells. Aurora kinase C, like Aurora kinase A and -B is also overexpressed in many cancer cells, even if only Aurora kinase A seems to be an oncogene. Although Aurora kinase B has not been demonstrated as an oncogene, increased level of histone H3 phosphorylation as a consequence of Aurora kinase B overexpression can induce aggressive tumours that develop metastasis in mice. Interestingly it was reported that Aurora kinase C overexpression also increases phosphorylation of Ser-10 in histone H3. The implication of Aurora kinase C in tumourigenesis has already been suggested because of a correlation between Aurora kinase C expression and the degree of dysplastic change in colorectal cancer cells. All together these results clearly suggest that Aurora kinase C does play a role in tumourigenesis when overexpressed.

Interestingly, the active form of Aurora -C displaces Aurora -A, in interphase but does not displace Aurora -B during division phase, showing its oncogenic role, probably linked to interphase rather than division phase.

Over expression of Aurora kinase C in cancerous tissues and cell lines also raises questions about its potential role in carcinogenesis and its effect on the proliferative capacity of tumour cells. The expression levels of Aurora kinase C, Aurora kinase B and Aurora kinase B splice variants are commonly altered in tumour cell lines and tissues. These alterations in expression have been associated with tumourigenesis, tumour metastasis and tumour aggression. All together, Aurora kinase C can be a novel excellent target of anticancer therapy

But, in this regard, what needs to be at least further explored are; What are the substrates of over expressed Aurora C, What is the expression profile of Aurora-C along cell cycle and How and to what extent Aurora-A/-B/-C compete with each other for their substrates.

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