EBioMedicine 25 (2017) 18–19

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Solid Cancer Treatment With Aurora Kinase Inhibitors: Towards a Personalized Medicine

Salvatore Ulisse

Department of Surgical Science, "Sapienza" University of Rome, Italy

Several mitotic proteins, whose expression or function has been found deregulated in human solid neoplasms, are thought to play a critical role in tumor genetic instability, a hallmark of cancer (Hanahan and Weinberg, 2011; Otto and Sicinski, 2017). These include the three serine/threonine Aurora kinase family members (Aurora A, B and C), involved in centrosome maturation, chromosome segregation and cytokinesis (Carmena and Earnshaw, 2003; Carmena et al., 2012).

The gene AURKA, encoding Aurora A, maps at the locus 20q13, frequently amplified in different cancer types. The gene AURKB, encoding Aurora B, is located at the locus 17p13, which harbours also the TP53 oncogene and often undergoes genetic aberrations in cancer resulting in the loss of p53 activity (Baldini et al., 2014). The upregulation of either Aurora A or B is thought to cause defects in chromosome segregation with consequent aneuploidy, and it has been shown to induce cell malignant transformation (Baldini et al., 2014). Furthermore, overexpression of Aurora kinases, observed in several cancer types, has been found to associate with a poor prognosis (Baldini et al., 2014; Tang et al., 2017; Kollareddy et al., 2012; Bavetsias and Linardopoulos, 2015). As a consequence, the Aurora kinases have been regarded as promising therapeutic targets for both solid and hematologic malignancies (Baldini et al., 2014; Tang et al., 2017; Kollareddy et al., 2012; Bavetsias and Linardopoulos, 2015). A number of either selective or pan-inhibitors of Aurora kinases have been developed over the last decade (Baldini et al., 2014; Tang et al., 2017; Kollareddy et al., 2012). However, despite the encouraging results in preclinical studies, clinical trials with different Aurora kinase inhibitors showed a limited efficacy against solid tumors, while higher response rates against hematologic malignancies were observed (Bavetsias and Linardopoulos, 2015). It has been speculated that such different outcome may be due to the higher homogeneity and higher proliferation rates observed in the hematologic malignancies relative to solid tumors (Bavetsias and Linardopoulos, 2015). Other possible causes of solid tumor resistance to aurora kinase inhibitors are emerging from preclinical studies (Kollareddy et al., 2012). Indeed, experiments performed on colon and pancreatic derived cell lines (SW620 and MiaPaca, respectively) treated for long period of time with the specific Aurora B inhibitor AZD1152, showed the development of clones of cancer cells in which drug accumulation in the cytoplasm was drastically reduced following the strong upregulation ATP-binding cassette transporters, such as ABCB1, ABCG2 and ABCC2 (Kollareddy et al., 2012). Similar observations were obtained with HeLa cells treated with the Aurora kinase inhibitor JNJ-7706621 (Kollareddy et al., 2012). In addition, treatment of the colon cancer derived cell line HCT116 with Aurora kinase inhibitor ZM447439 for 1 month, it has been shown to lead to the selection of clones of malignant cells characterized by mutations in Aurora kinase genes detrimental to the efficient binding of the inhibitor in the ATP pocket of the enzyme (Kollareddy et al., 2012). While these observations will need to be confirmed in clinical trials, the identification of molecular markers capable to predict patients' response to treatment with the Aurora kinase inhibitors is highly required.

In the present issue of *EBioMedicine*, Niu and colleagues identified an additional molecular mechanism that could contribute to the observed resistance of solid tumors to Aurora kinase inhibitors (Niu et al., 2017). The authors evaluated the clinical significance of two Aurora A functional single nucleotide polymorphisms (SNP) at codon 31 [F/I] and codon 57 [V/I] on patients' survival, and their ability to predict the clinical outcome of patients with solid tumors treated with the selective Aurora A inhibitor alisertib (MLN8237) (Niu et al., 2017). In particular, the two Aurora A SNPs were evaluated as predictive biomarkers for clinical outcomes of patients treated with alisertib in two phase 2 clinical trials. In the first, the Aurora A SNPs were analysed in 85 patients with advanced solid tumors receiving single-agent alisertib, while in the second, 122 patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer were treated with alisertib plus paclitaxel ($n = 62$) or paclitaxel alone ($n = 60$). Among the 85 patients treated with alisertib, those carrying the VV alleles at codon 57 (62%) had significantly longer progression-free survival (PFS) than patients carrying the VI or II alleles. Similarly, in the second clinical trial patients with the VV alleles at codon 57 who received alisertib plus paclitaxel (39%) had a trend towards an improved PFS, with respect to those treated with paclitaxel alone. On the other hand, the authors could not find any association between SNP at codon 31 and response to alisertib therapy (Niu et al., 2017).

These observations suggest that SNP at codon 57 of the AURKA gene may turn useful for the identification of patients who may benefit from alisertib treatment, avoiding a useless treatment to the others. Although these results should be corroborated in larger case-studies, they pave the way for a better selection of patients to be treated with alisertib, and may provide useful information for other Aurora kinase inhibitors under clinical evaluation.

DOI of original article: https://doi.org/10.1016/j.ebiom.2017.10.015.
E-mail address: salvatore.ulisse@uniroma1.it (S. Ulisse).

https://doi.org/10.1016/j.ebiom.2017.10.026
2352-3964/© 2017 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Disclosure

The author declared no conflicts of interest.

References

Baldini, E., D'Armiento, M., Ulisse, S., 2014. A new aurora in anaplastic thyroid cancer therapy. J Endocrinol]–>Int. J. Endocrinol. 2014, 816430.

Bavetsias, V., Linardopoulos, S., 2015. Aurora kinase inhibitors: current status and outlook. Front. Oncol. 5, 278.

Carmena, M., Earnshaw, W.C., 2003. The cellular geography of aurora kinases. Nat. Rev. Mol. Cell Biol. 4 (11), 842–854.

Carmena, M., Wheelock, M., Funabiki, H., Earnshaw, W.C., 2012. The chromosomal passenger complex (CPC): from easy rider to the godfather of mitosis. Nat. Rev. Mol. Cell Biol. 13 (12), 789–803.

Hanahan, D., Weinberg, R.A., 2011. Hallmarks of cancer: the next generation. Cell 144 (5), 646–674.

Kollareddy, M., Zheleva, D., Dzubak, P., Brahmkshatriya, P.S., Lepsik, M., Hajduch, M., 2012. Aurora kinase inhibitors: progress towards the clinic. Investig. New Drugs 30 (6), 2411–2432.

Niu, H., Shin, H., Gao, F., et al., 2017. Aurora A functional single nucleotide polymorphism (SNP) correlates with clinical outcome in patients with advanced solid tumors treated with alisertib, an investigational Aurora A kinase inhibitor. EBioMedicine 25, 50–57.

Otto, T., Sicinski, P., 2017. Cell cycle proteins as promising targets in cancer therapy. Nat. Rev. Cancer 17 (2), 93–115.

Tang, A., Gao, K., Chu, L., et al., 2017. Aurora kinases: novel therapy targets in cancers. Oncotarget 8 (14), 23937–23954.