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Review

The Role of Speedy/RINGO Protein in Breast Cancer as a Future Biomarker

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Abstract. *Background/Aim: Cyclin-dependent kinases (CDKs) are proteins that require the binding of regulatory subunits called cyclins and play a key role in cell cycle progression and activation. CDKs play a key role in carcinogenesis of many solid malignancies, and inhibition of these proteins has produced anti-cancer effects demonstrated in preclinical studies. This narrative review was conducted to develop a hypothetical approach to determine whether Speedy/RINGO, a protein associated with CDK2, could be a possible predictive factor in breast cancer patients treated with a CDK4/6 inhibitor. Materials and Methods: A literature search was conducted in PubMed, Web of Science, Medline, and Google Scholars search engines to match the following words: "Speedy/RINGO" or "Spy1" and "CDKs" or "Cyclin-dependent kinases (CDKs)" and "CDK4/6 inhibitors" and "Regulation" and "Molecular" and "Breast cancer" and "Carcinogenesis". Only articles investigating the relationship between the Speedy/RINGO protein and CDKs at the molecular level were included. Literature information was compiled by trying to establish a relationship with our hypothesis question. Results: Speedy/RINGO is a tightly regulated proto-oncogenic mammalian protein playing important roles in the somatic cell cycle. Studies have emphasized that although it does not have amino acid sequence homology with cyclins, it can activate CDK2. In addition, results showing molecular compensation of CDK4/6 inhibition through CDK2 activation, also showed that CDK2 can predict drug resistance. Another important finding was that overexpressed Speedy/RINGO, during CDK4/6 inhibitor treatment, could strongly activate CDK2, resulting in a negative response to treatment. Conclusion: Although many predictive factors have been investigated to indicate response to CDK4/6 inhibitors or determine drug resistance, a consensus biomarker has yet to be established. In light of the information obtained from our review, it can be concluded that the Speedy/RINGO protein may have an important role as a predictive biomarker in terms of response to treatment, continuity of treatment and drug resistance in patients treated with CDK4/6 inhibitors.*

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Almost all human cancers have abnormalities in the cyclin D/cyclin dependent kinases4/6 (CDK4/6) pathway, which plays an important role as a cell cycle control point. This pathway is in tight relationship with retinoblastoma protein (pRb)-E2F that is the major regulatory complex of cell cycle, and hence CDK4/6 complexes are currently important targets for cancer treatment (1).

Despite rapid advances in treatment options, breast cancer, which is a heterogeneous malignancy, is still among the leading causes of cancer death (2). Following molecular studies conducted on hormone resistance in metastatic estrogen/progesterone receptor (HR+) positive, and human epithelial growth factor receptor2 (HER2–) negative breast cancer, CDK4/6 inhibitors administered in monotherapy or combination with aromatase inhibitors or fulvestrant have become the subject of remarkable studies (3-8). The positive

and significant increase in progression-free survival in clinical trials of three different CDK4/6 inhibitors, namely ribociclib, palbociclib, and abemaciclib, enabled these three inhibitors to be quickly included in international treatment guidelines (3-8). Clinical trials introduced three different CDK4/6 inhibitors available in treatment guidelines: palbociclib, ribociclib, and abemaciclib. Of these, palbociclib and ribociclib have been approved by the Food and Drug Administration (FDA) in combination with letrozole, an aromatase inhibitor in the first-line treatment of HR+, HER2– advanced or metastatic patients with postmenopausal breast cancer (3-5). In the PALOMA-2 study, palbociclib plus letrozole *vs*. placebo plus letrozole treatments were compared (4). MONALEESA-2 compared ribociclib plus letrozole *vs*. placebo plus letrozole. The effectiveness of these agents with monotherapy is limited and considered cytostatic (5). Following the studies of MONARCH-1 and MONARCH-2, abemaciclib received FDA approval both in monotherapy and combination with fulvestrant in progression under endocrine therapy in patients with HR+, HER2- metastatic breast cancer (6, 7). Finally, after the positive results of the MONARCH-3 study, abemaciclib was also approved for the same patient group in combination with the aromatase inhibitor (8).

In addition, studies have shown that CDK4/6 inhibitors induce apoptosis in some tumor types (1, 6). However, in some cases, CDK2 is shown to compensate and reverse the effect of CDK4/6 inhibition resulting in drug resistance (4). Thus, today, a clear biomarker that predicts the importance of drug resistance or treatment responses has not yet been identified (1).

At this point, one of the activating partners of CDK2, Speedy/RINGO (Spy1) draws attention. Spy1 is an unconventional cell-cycle regulatory protein which controls G_1/S transition by activating CDK2. Spy1 is shown to be an oncogenic protein which triggers carcinogenesis when overexpressed in certain cancers such as breast cancer (2). Combining CDK2 activating function of Spy1 and observed CDK2 activation during CDK4/6 inhibitory treatment forced us to think if Spy1 could be the cause of this CDK2 activation, and if Spy1 could be a predictive biomarker to predict the patient's response to CDK4/6 inhibitor treatment.

Although some predictive factors have been investigated to indicate response to CDK4/6 inhibitors or determine drug resistance, a consensus biomarker has not yet been established. Therefore, we emphasized in the hypothesis that Spy1 protein may be a predictive factor for the use of CDK4/6 inhibitors in HR+/HER2-breast cancer (1). This narrative review was conducted to develop a hypothetical approach to determine whether Speedy/RINGO, a protein associated with CDK2, could be a possible predictive factor in breast cancer patients treated with a CDK4/6 inhibitor.

Materials and Methods

For this study, a literature search was conducted employing the PubMed, Web of Science, Medline, and Google Scholar search engines using the following search terms: "Speedy/RINGO" or "Spy1" and "CDKs" or "Cyclin-dependent kinases (CDKs)" and "CDK4/6 inhibitors" and "Regulation" and "Molecular" and "Breast cancer" and "Carcinogenesis". Only full-text articles in English were searched regarding the relationship between the Speedy/RINGO protein and CDKs at the molecular level. Studies whose full texts were available and whose results reflected the possible molecular relationship between Speedy/RINGO, CDK2 and CDK4/6, were thoroughly investigated. A figure related to PRISMA-like analysis that shows the steps of the article selection process has not been created. Instead, the information in the articles obtained by using relevant words was evaluated in accordance with our hypothesis question. The information obtained from the literature review was compiled by giving appropriate subheadings to explain our hypothesis.

Results and Discussion

The basis of the compensatory interaction between CDK4/6 and CDK2. Although inhibition of CDK4/6 with drugs such as palbociclib is a significant treatment strategy, studies show that lost CDK4/6 activity can be tolerated by CDK2, and thus the S phase transition continues with pRb phosphorylation pointing out acquired drug resistance (9). Examining the mechanism of this process reveals that the P27Kip1 cell cycle inhibitor has a significant role. Under normal conditions, the unphosphorylated-p27Kip1 binds to the cyclin D-CDK4 complex, thereby preventing this complex from phosphorylating pRb protein. However, when p27Kip1 is phosphorylated through its Y88 residue, it is detached from the complex and the released cyclin D-CDK4 performs pRb phosphorylation permitting S phase transition (9, 10). However, in case of suppression of this system by CDK4/6 inhibitors, CDK2 is activated as an alternative way and cyclin E-CDK2 complex is formed. However, this complex is inhibited when attached to phosphorylated- or unphosphorylated-p27 and cannot perform pRb phosphorylation. However, if it is connected to Y88 phosphorylated-p27, Y88 p27-cyclin E-CDK2 complex phosphorylates p27 over its T187 residue, which causes p27 to dissociate from the complex. As a result, cyclin E-CDK2 phosphorylates pRb and drives S phase transition (9, 10).

All these data show that compensatory increase in CDK2 observed during the use of CDK4/6 inhibitors will decrease the effectiveness of treatment and may be an indication of acquired drug resistance (9). This indicates that cancer types with intrinsic Speedy/RINGO protein over-expression (some types of breast cancer, neuroblastoma, *etc*.) also have intrinsically increased CDK2, so that the inhibition of CDK4/6 can more easily be tolerated in these cancers (9). Thus, it may be a prognostic marker for the effectiveness of treatment with drugs such as palbociclib. Studies have also shown that Speedy/RINGO does not need phosphorylation with CDK-activating kinase (CAK) for

CDK2 activation and is insensitive to inhibitors such as p27Kip1 (9). This will also be prominent and decisive for the emerging strategy of the co-inhibition of CDK2 and CDK4/6 by preventing p27Kip1 phosphorylation in order to hinder drug resistance, since existing and potential inhibitors can act directly on CDK4/6 as well as on p27Kip1 (9).

Speedy/RINGO protein and its functions. Although cyclins play a key role in regulating CDK activity, a new family of Speedy/RINGO proteins has been identified that can regulate the cell-cycle more efficiently than cyclins (11).

Speedy/RINGO is a new family of proteins that were first identified in Xenopus oocytes and were found to be required for meiotic oocyte maturation (12). It has been reported that oocytes in the resting phase are restricted in the G_2/M phase of the first meiotic division. Speedy/RINGO has been reported to be sufficient to stimulate and accelerate G_2/M progress for meiotic oocyte maturation (11, 12). Speedy/RINGO is a cell cycle regulator that can activate CDKs although it does not show sequence homology with any known cyclin (11). In addition, activation of the Speedy/RINGO-CDK complexes does not require an activating phosphorylation by the CAK which is required for all other known cyclins (13).

The existence of a central region called Speedy/RINGO box with 51-67% homology among family members has been identified in all six Speedy/RINGO proteins (13). This region is required for the binding of CDKs (11, 12). Speedy/RINGO A is the slowest growing and most protected branch of the Speedy/RINGO, also defined as the oldest branch. It is expressed in various tissues in mammals and Spy1 protein, a cell cycle regulator encoded by the *Speedy/RINGO* A gene, has been shown to control CDK2 activity and G_1/S phase transition (12, 13). In addition, study results of multiple immortalized cell systems have shown that over-expression of Spy1 leads to shortening of the G_1/S phase in the cell cycle, CDK2 activation, p27Kip1 disruption and ultimately increases cell proliferation (14-18). Therefore, Spy1 has been shown to play a key role in regulating both cell growth and apoptosis (15-18). Furthermore, Spy1 protein plays an important role in the progression of neuroblastoma *via* both CDK2 and p27Kip1. Therefore, it is obvious that Speedy/RINGO protein directs tumor formation of neuroblastoma cells (14).

Speedy/RINGO protein and breast cancer. It has been reported that critical levels of Spy1 protein led to CDK1 activation and this mechanism is also sensitive to the inhibitory effect of the apoptotic regulator *FOXO1*. This protein, which regulates the cell cycle independently of cyclin binding by activating CDKs, is predicted to promote rapid cell cycle progression during the G_1/S phase (15). Studies in hepatocarcinoma have shown that overexpression of the Spy1 protein promotes tumorigenesis in mouse models (16). Subsequent breast cancer studies have reported a significant association between proliferation in normal breast tissue and increased Spy1 protein levels. It has also been shown that this protein can be expressed at different levels in invasive carcinoma of the breast and ductal carcinoma *in situ*. The idea that down-regulation of Spy1 can significantly inhibit breast cancer cell growth is associated with this mechanism based on basic knowledge and research results (17, 18). Although Spy1 levels have been shown to be high in all proliferative normal breast tissue, it has been reported that increased levels are mostly in invasive lobular carcinoma and the most significant changes in protein levels are found in intraductal carcinoma. It was also found to be particularly high in the aggressive MDA-231 cell line. In contrast, Spy1 has also been shown to be significantly less expressed than MDA-231 cells in the slower growing MCF7 breast cancer series (17, 18).

Basic biology of CDKs. There are several interactions of various molecules, such as growth factors and hormones, in the progression of the cell cycle resulting in cell division which is a tightly controlled mechanism (19). CDKs are known to play an important role in cell cycle control by regulating checkpoints with the assistance of their interacting and activating partners, cyclins (20). The first checkpoint is also known as the restriction point, and completion of the cell cycle resulting from this pause in the G_1-S transition was determined to be independent of the stimuli of the mitogens (19).

A cell exposed to mitogenic stimuli activates both CDK4 and CDK6 by synthesizing cyclin D during the G_1 phase (19). CDK4/6, complexing with cyclin D, catalyzes the monophosphorylation of the pRb which is a protein that inhibits E2F transcription factors in its hypophosphorylated form. As a result of this monophosphorylation, cyclin E levels increase and the resulting cyclinE-CDK2 complex causes pRb to be hyperphosphorylated in 14 distinct regions which leads to the release of pRb from E2F and setting E2F free for the transcription of certain genes necessary to progress to the S phase, such as *cyclin E* gene (CCNE) and c-myc. The second checkpoint operates at the G_2-M transition and is controlled by the CDK1-cyclin B complex, while the S-G_2 transition needs the formation of CDK2-cyclin A and CDK1-cyclin A complexes (19, 20).

CDKs have been shown to be negatively regulated by proteins including INK4 and CIP/KIP family members. The INK4 family has been reported to consist of p16INK4A, p15INK4C, p18INK4C and p19INK4D inhibitor proteins. Their main function has been shown to inhibit the phosphorylation of pRb by binding to CDK4 and CDK6 through competing with cyclins which causes cell cycle to stop at G_1. In contrast, the CIP/KIP family containing p21CIP1 and p27KIP1 can bind and inhibit many different CDK-cyclin complexes, thereby having a different effect on the cell cycle (20). p21CIP1 which is an important transcriptional target of *P53* regulates CDK2- cyclin E activity, allowing the cell cycle

to stop at G_1 and G_2 in case of DNA damage. p27KIP1 was determined to inhibit the activity of CDK4-cyclin D and CDK2-cyclin E complexes in G_1 phase (20).

It has been reported that the cell cycle regulatory factor Spy1 activates ERK1/2 through positive feedback in a MEK-independent manner. Mitogenic signals from receptor tyrosine kinases and downstream signaling pathways, such as RAS, phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), mammalian target of rapamycin (mTOR), and nuclear receptors (estrogen receptor, progesterone receptor, and androgen receptor) directs the progression of cells from the G_0 or G_1 phase to the S phase *via* the CDK4 or CDK6 complex (1, 6, 20).

Relation of CDK4/6-cyclin D-Rb-E2F axis dysregulation with carcinogenesis. Although varying depending on cell type and localization of cancer, 40% of all human cancers have been shown to have changes in the expression and activities of cyclins and CDKs as well as CDK modulators resulting in continuous cell proliferation. Amplification of the *cyclin D1* gene (*CCND1*) and increased expression of cyclin D1 protein were observed in more than 50% of esophageal carcinomas, whereas amplification of the *CDK4* gene is detected in many types of cancer, including melanoma, malignant glioma, and sarcoma. However, amplification of the CDK6 is reported to be more common in head and neck, gastric, pancreatic, and esophagus cancers (21, 22).

Possible recommendations of the hypothetical perspective for future research on response and drug resistance to CDK inhibitors. In the absence of pRb, there is no longer need for CDK4/6 to progress the cycle through S phase, but cell cycle can still progress alternatively with the help of E2F and cyclin E-CDK2 (23). In this case, CDK4/6 inhibitors cannot have any therapeutic effect. Considering this, it can be thought that the use of cyclin E-CDK2 inhibitors together with CDK4/6 inhibitors in the absence of *Rb* may eliminate drug resistance. On the other hand, there is a prevailing opinion that results from clinical studies on CDK4/6 inhibitors are inconsistent with preclinical studies (23, 24). Indeed, amplification of the *CCND1* (cyclin D1 encoding) and lack of the *CDKN2A* (p16 encoding) were shown not to be associated with susceptibility to palbociclib in breast cancer patients. However, the results of studies on different types of cancers have identified a subgroup with a genomic feature called "D-cyclin Activated Properties" in relation to susceptibility to abemaciclib (23, 24). These alternative genomic features have been reported to include many genetic alterations, such as changes in *cyclin D*, loss of *cyclin K*, and lack of *F-box protein31* (1, 23, 24). On the other hand, studies on pan-cancer dataset have shown that cyclin E/pRb complex correlates better for palbociclib than cyclin E or pRb only and has increased IC_{50} levels. With these results, it was concluded that the *CCNE1*/*RB1* ratio can distinguish between susceptibility and resistance to palbociclib (24).

Some molecular alterations, such as acquired pRb mutations, pRb loss, loss of FAT-1 functional mutations, overexpression of CCNE1, and overexpression in CDK6, as well as CCNE1/Rb1 ratio are various mechanisms related to acquired drug-resistance with long-term usage of CDK4/6 inhibitors (1, 13). However, a strong biomarker predicting response to CDK4/6 inhibitors has not yet been identified and molecular studies seem to be ongoing (23, 24).

In breast cancer studies, it has been demonstrated that Rb1 must be intact for CKD4/6 inhibitors to affect cell-cycle progression. Rb1-mutant cancers are resistant to CKD4/6 inhibitors. Increased activity through mitogenic signaling pathways, such as PI3K, mTOR, steroid receptor pathways also result in activation of cyclin D-CDK 4/6 activity. This situation has been envisaged as a basis for drug resistance mechanisms.

Conclusion

Spy1 is a novel protein whose importance in carcinogenesis, prognosis and response to treatment is being further investigated with hypothetical approaches based on the presence of cell-cycle abnormalities in many cancer types. Results of molecular studies suggesting that CDK2 activation is reduced in the presence of overexpression of Speedy/RINGO suggest that this protein plays a key role in cell cycle control. Proliferative interaction with CDK4/6 and resistance interaction with CDK2 have been shown in many studies. In light of this information, we propose that Speedy/RINGO protein has an important role as a predictive biomarker for patients treated with CDK4/6 inhibitors in terms of response to treatment, continuity of treatment and drug resistance.

Conflicts of Interest

The Authors declare no competing interests.

Authors' Contributions

All Authors have contributed to this work and approved the final version of the manuscript.

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