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PIK3R2 is an Oncogene and a Predictor of Response to Tyrosine Kinase Inhibitors in Ovarian Cancer

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Abstract

The p85 regulatory subunits of the Phosphoinositide 3-Kinase (PI3K), which include p85α and p85β, interact with the Receptor Tyrosine Kinases (RTKs) and the p110 catalytic subunits for PI3K pathway activation. High levels of *PIK3R2*/p85β correlate with worse patient survival in ovarian cancer. Investigations are warranted to understand the regulatory role and pathogenic role of p85β in pathway activation and cancer development, respectively. Recently, we have revealed the molecular mechanisms through which p85β induces ovarian tumorigenesis. Remarkably, these oncogenic mechanisms create exploitable vulnerabilities to targeting of the RTKs.

Introduction

Ovarian cancer is the most lethal gynecologic cancer and the third most common gynecologic malignancy worldwide. The Receptor Tyrosine Kinases (RTKs), such as the Human Epidermal Growth Factor Receptor (HER) family and AXL, are often activated in ovarian cancer, suggesting that these RTKs might represent promising therapeutic targets. However, challenges remain in utilizing different Tyrosine Kinase Inhibitors (TKIs) in ovarian cancer patients either as a single agent or in combinational therapeutic regimens with other agents [1]. The reasons for this lack of efficacy remain to be fully unraveled. The Phosphoinositide 3-Kinase (PI3K)/AKT/mTOR pathway is frequently altered in ovarian cancer. Interestingly, co-targeting Epidermal Growth Factor Receptor (EGFR) and the PI3K pathway has been previously shown to produce synergistic antitumor effects in the disease [2]. p85β is the regulatory subunit of PI3K. We have recently reported that p85β is an oncogenic factor that promotes the acquisition of tumorigenic phenotypes [3]. We also explored the interaction between p85β and RTKs (EGFR and AXL) in ovarian cancer cells. These data shed light on the design of rational targeted therapies for *PIK3R2*-amplified or p85β-overexpressing ovarian tumors.

Low p85β level associates with EGFR-TKI resistance through DNA damage repair

Drug resistance to EGFR TKIs is common in cancers. EGFR secondary mutations and bypass signaling activations are two central mechanisms in mediating the resistance. In an EGFR-dependent manner, an acquired mutation interferes with the binding of TKIs to the EGFR kinase domain. In an EGFR-independent manner, dysregulation of other RTKs or activation of downstream signaling components triggers compensatory action against the TKIs *via* inducing PI3K/AKT or Mitogen-Activated Protein Kinase (MAPK) signaling [4]. Further investigations are warranted to evaluate the mechanism of resistance to EGFR inhibition in ovarian cancer and to derive rational combination therapies accordingly. It has previously been demonstrated that expression of *PIK3R3* (p55γ) was reduced in sensitive glioma cell lines after EGFR inhibition by erlotinib, suggesting *PIK3R3* as a marker for response to erlotinib [5]. Interestingly, in our recent study, we found that unlike *PIK3CA* (p110α) and *PIK3CB* (p110β), ovarian cancer cells that were relatively sensitive to erlotinib had higher p85β protein levels than resistant cells [6]. Overexpressing *PIK3R2* rendered cells higher sensitivity to erlotinib, whereas depletion of *PIK3R2* led to erlotinib resistance. Erlotinib sensitivity was independent of *PIK3R3* and other isoforms (*PIK3R1*, *PIK3CD*, and *PIK3CG*) in ovarian cancer.

Recent studies have indicated an interaction between the EGFR pathway and DNA Damage Response (DDR) following drug treatments [7,8]. Although p85 may participate in the cell death process induced by oxidative stress [9], p85 was not known to modulate DNA damage repair. We reported that depletion of *PIK3R2* increased DNA damage and decreased level of the non-homologous end joining DNA repair protein BRD4, resulting in defective DDR [6]. Intriguingly, DNA damage was further exacerbated in *PIK3R2*-depleted cells upon erlotinib treatment because erlotinib alone also attenuated DNA repair. However, whether the effect of p85β on DDR involves

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the canonical PI3K signaling remains to be examined. It would be interesting to further identify the other proteins that participate in DDR in the *PIK3R2*-depleted cells.

Erlotinib treatment of the *PIK3R2*-depleted cells increased the phosphorylation and nuclear import of p38 MAPK with an accompanying decrease in the amount of DNA damage. Our results are consistent with the role of p38 MAPK in DNA repair. It has been reported that nuclear translocation of p38 MAPK in response to DNA damage was triggered by phosphorylation within the active site to induce DNA repair [10]. Also, p38 MAPK activation occurred in response to inhibition of EGFR/HER2 in bladder cancer [11]. Further, our study showed that p38 MAPK was activated as an outcome of both p85β depletion and erlotinib treatment but not in a single event, suggesting the existence of threshold which allows for p38 MAPK activation. Remarkably, our drug response data revealed that the combination of erlotinib and p38 inhibitor significantly achieved a synergetic effect on reducing tumor burden. Future studies are needed to fully validate the combination strategy to overcome the erlotinib resistance in ovarian cancer. In light of these findings, p85β level could be a potential biomarker of responsiveness to EGFR inhibitor therapy in ovarian cancer. It is important to emphasize that while our data demonstrated increased erlotinib sensitivity upon *PIK3R2* overexpression, whether these cells are sensitive to erlotinib through an opposite mechanism exhibited by the resistant cells is unknown. In this regard, in contrast to the *PIK3R2*-depleted cells which had reduced BRD4 levels, ovarian tumor samples with *PIK3R2* amplification did have higher BRD4 protein levels than the diploid counterpart [6]. Nonetheless, the mechanism underlying the increased erlotinib sensitivity awaits investigation.

p85β-overexpressing cells shows increased AXL level and sensitivity to AXL-TKI

PIK3R2 level may also predict sensitivity towards inhibitors of AXL, which is another RTK that has been implicated in ovarian pathogenesis [12]. AXL belongs to the Tyro/Axl/Mer (TAM) family of RTKs. Increased expression of AXL has been shown in many cancers, including that of the ovary, lung, breast, pancreas, and prostate [13-17]. Our recent data revealed that p85β sensitized cells to inhibition of AXL signaling, suggesting *PIK3R2* amplification or p85β level as a potential biomarker in response to anti-AXL therapy in ovarian cancer [3].

p85 can indirectly bind to AXL *via* an interaction between the proline-rich region of p85 and the N-terminal SH3 domain of Grb2 [18]. Our investigations showed that p85β upregulated the protein level of AXL through inhibiting the autophagy-lysosomal degradation pathway that would otherwise induce AXL protein degradation. Another major observation in our study was the specific regulation of AXL because the other two TAM members (Tyro3 and MERTK) were not altered by p85β, implying the specific potential of targeting AXL in tumors with increased p85β levels. We showed that blockade of AXL substantially inhibited AKT-independent PDK1/SGK3 signaling to promote oncogenic phenotypes [3]. Along this line, *PIK3CA* mutant breast cancer cells exhibited only minimal AKT activation but a dependency on SGK3 for anchorage-independent growth [19]. It is noteworthy that an association of AXL and EGFR family members has been previously proposed [20,21]. In our study, inhibition of EGFR by neither lapatinib nor erlotinib had any influence on the induction of AXL by p85β, suggesting that the activation of AXL is unlikely to occur through an interaction with the HER family. However, we are uncertain if AXL activation by p85β has any influence on EGFR-TKI response.

Conclusion

Our research has identified previously unknown mechanisms driven by p85β that contributes to ovarian tumorigenesis and responses to TKIs in ovarian cancer. The copy number status or expression levels of *PIK3R2* may affect treatment response to EGFR and AXL inhibitors. These findings are significant given the frequent *PIK3R2* overexpression or amplification in ovarian cancer particularly the serous subtype. *PIK3R2* could be a predictive biomarker to select patients who may show clinical benefit to these TKIs. Yet, better definition and characterization of the signaling network of p85β will determine the optimal therapeutic approach for *PIK3R2*-overexpressing ovarian tumor.

Activation of multiple RTKs is involved in ovarian cancer pathogenesis. It is highly likely that the tumor transformation is dependent on the coordinated activity of multiple RTKs instead of an individual RTK oncoprotein. So far, there appears to be little success of single TKI treatment in ovarian cancer clinically. In light of the findings described above, it would be interesting to explore whether simultaneous inhibition of multiple RTKs causes greater anti-tumor effect than inhibition of individual activated RTK in ovarian cancer patients with *PIK3R2* amplification.

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