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Cancer Letters

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Small molecule inhibition of TFF3 overcomes tamoxifen resistance and enhances taxane efficacy in ER+ mammary carcinoma

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Abstract

Even though tamoxifen has significantly improved the survival of estrogen receptor positive (ER+) mammary carcinoma (MC) patients, the development of drug resistance with consequent disease recurrence has limited its therapeutic efficacy. Trefoil factor-3 (TFF3) has been previously reported to mediate anti-estrogen resistance in ER+MC. Herein, the efficacy of a small molecule inhibitor of TFF3 (AMPC) in enhancing sensitivity and mitigating acquired resistance to tamoxifen in ER+MC cells was investigated. AMPC induced apoptosis of tamoxifen-sensitive and resistant ER+MC cells and significantly reduced cell survival in 2D and 3D culture *in vitro*. In addition, AMPC reduced cancer stem cell (CSC)-like behavior in ER+MC cells in a BCL2-dependent manner. Synergistic effects of AMPC and tamoxifen were demonstrated in ER+MC cells and AMPC was observed to improve tamoxifen efficacy in tamoxifen-sensitive cells and to re-sensitize cells to tamoxifen in tamoxifen-resistant ER+MC *in vitro* and *in vivo*. Additionally, tamoxifen-resistant ER+MC cells were concomitantly resistant to anthracycline, platinum and fluoropyrimidine drugs, but not to Taxanes. Taxane treatment of tamoxifen-sensitive and resistant ER+MC cells increased TFF3 expression indicating a combination vulnerability for tamoxifen-resistant ER+MC cells. Taxanes increased CSC-like behavior of tamoxifen-sensitive and resistant ER+MC cells which was reduced by AMPC treatment. Taxanes synergized with AMPC to promote apoptosis and reduce CSC-like behavior *in vitro* and *in vivo*. Hence, AMPC restored the sensitivity of tamoxifen and enhanced the efficacy of Taxanes in tamoxifen-resistant ER+MC. In conclusion, pharmacological inhibition of TFF3 may serve as an effective combinatorial therapeutic strategy for the treatment of tamoxifen-resistant ER+MC.

Introduction

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Research paper

Discovery of imidazopyridine-pyrazoline-hybrid structure as SHP-1 agonist that suppresses phospho-STAT3 signaling in human breast cancer cells

Min Hee Yang [a 1], Gautam Sethi [b 1], Akshay Ravish [c], Arun Kumar Mohan [c], Vijay Pandey [d], Peter E. Lobie [d e f], Shreeja Basappa [g], Basappa Basappa [c], Kwang Seok Ahn [a]

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Abstract

Signal transducer and activator of transcription 3 (STAT3) promotes breast cancer malignancy and controls key processes including proliferation, differentiation, and survival in breast cancer cells. Although many methods for treating breast cancer have been improved, there is still a need to discover and develop new methods for breast cancer treatment. Therefore, we synthesized a new compound 2-(4-(2,3-dichlorophenyl)piperazin-1-yl)-1-(3-(2,6-dimethylimidazo[1,2-a]pyridin-3-yl)-5-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (DIP). We aimed to evaluate the anti-cancer effect of DIP in breast cancer cells and clarify its mode of action. We noted that DIP abrogated STAT3 activation and STAT3 upstream kinases janus-activated kinase (JAK) and Src kinases. In addition, DIP promoted the levels of SHP-1 protein and acts as SHP-1 agonist. Further, silencing of SHP-1 gene reversed the DIP-induced attenuation of STAT3 activation and apoptosis. DIP also induced apoptosis through modulating PARP cleavage and oncogenic proteins. Moreover, DIP also significantly enhanced the apoptotic effects of docetaxel through the suppression of STAT3 activation in breast cancer cells.

Overall, our data indicated that DIP may act as a suppressor of STAT3 cascade, and it could be a new therapeutic strategy in breast cancer cells.

Introduction

Breast cancer is the most prevalent malignancy and commonly diagnosed cancer in women over the world [1,2]. The incidence of breast cancer in women has been gradually increasing by about 0.5% per year since the mid-2000s [3]. Patients are generally treated by using chemotherapy, radiotherapy, and surgical

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Vertical pathway inhibition of receptor tyrosine kinases and BAD with synergistic efficacy in triple negative breast cancer

Yan Qin Tan[1,2,10], Yi-Shiou Chiou[2,3,4,5,10], Hui Guo[2], Shuwei Zhang[2], Xiaoming Huang[1,2,4], Dukanya Dukanya[6], Arun M. Kumar[6], Shreeja Basappa[6], Suling Liu[7], Tao Zhu[4,8,9], Basappa Basappa[6]✉, Vijay Pandey[1,2]✉ and Peter E. Lobie[1,2,4]✉

Aberrant activation of the PI3K/AKT signaling axis along with the sustained phosphorylation of downstream BAD is associated with a poor outcome of TNBC. Herein, the phosphorylated to non-phosphorylated ratio of BAD, an effector of PI3K/AKT promoting cell survival, was observed to be correlated with worse clinicopathologic indicators of outcome, including higher grade, higher proliferative index and lymph node metastasis. The structural optimization of a previously reported inhibitor of BAD-Ser99 phosphorylation was therefore achieved to generate a small molecule inhibiting the phosphorylation of BAD at Ser99 with enhanced potency and improved oral bioavailability. The molecule 2-((4-(2,3-dichlorophenyl)piperazin-1-yl)(pyridin-3-yl)methyl) phenol (NCK) displayed no toxicity at supra-therapeutic doses and was therefore assessed for utility in TNBC. NCK promoted apoptosis and G0/G1 cell cycle arrest of TNBC cell lines in vitro, concordant with gene expression analyses, and reduced in vivo xenograft growth and metastatic burden, demonstrating efficacy as a single agent. Additionally, combinatorial oncology compound library screening demonstrated that NCK synergized with tyrosine kinase inhibitors (TKIs), specifically OSI-930 or Crizotinib in reducing cell viability and promoting apoptosis of TNBC cells. The synergistic effects of NCK and TKIs were also observed in vivo with complete regression of a percentage of TNBC cell line derived xenografts and prevention of metastatic spread. In patient-derived TNBC xenograft models, NCK prolonged survival times of host animals, and in combination with TKIs generated superior survival outcomes to single agent treatment. Hence, this study provides proof of concept to further develop rational and mechanistic based therapeutic strategies to ameliorate the outcome of TNBC.

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INTRODUCTION

With the lack of expression of estrogen receptor (ER), progesterone receptor (PR) and lack of amplification of human epidermal growth factor receptor 2 (HER2), chemotherapy is currently the main systemic therapeutic option for TNBC. Even though patients with TNBC generally showed a better response to chemotherapy than other BC subtypes, TNBC patients often exhibit a significantly different response towards conventional therapy due to heterogeneity and distinct differences in pathway activation[1,2]. The phosphoinositide 3-kinase (PI3K)/AKT pathway is among the most important intracellular signaling cascades in cancer and plays a pivotal role in linking receptor tyrosine kinases (RTKs), a transmembrane protein family with intrinsic tyrosine kinase activity, to cancer development and progression[3]. With the frequent activation of PI3K/AKT signaling[4–6], TNBC has been reported to be sensitive to the PI3K/mTOR inhibitor NVP-BEZ235 irrespective of PIK3CA mutation or PTEN deficiency, raising the possibility of targeting this axis for treatment[7]. However, even though pre-clinical data indicate the potency of targeting the PI3K/AKT pathway in TNBC, intra-pathway feedback loops caused by single kinase inhibition along the PI3K/AKT axis and toxicity associated with PI3K/AKT/mTOR dual-blockade agents potentially limit their effectiveness in the clinic. Therefore, it is essential to identify novel therapeutic approaches to improve the prognosis of TNBC.

BCL2-associated death promoter (BAD) is a BH3-only member of the BCL-2 family governing apoptosis and BAD phosphorylation is increased in various cancers[8]. By phosphorylation at human Ser75, Ser99 and Ser118, BAD switches from pro-apoptotic functions to promotion of cell survival, by heterodimerizing with 14-3-3 protein instead of BCL-XL, BCL-2 or BCL-w[8,9]. In addition to its apoptotic function, a role of BAD in inhibiting G1 to S phase transition and CYCLIN D1 expression were previously reported[10]. Being a core downstream molecule of the PI3K/AKT and MAPK pathways, BAD phosphorylation at the Serine 99 residue, and subsequently at Serine 118, is governed by the activation of PI3K/AKT whereas BAD phosphorylation at Serine 75 residue is predominantly achieved by the MAPK pathway[11]. Not surprising given the aberrant activation of the PI3K/AKT pathway in TNBC, high pBADSer99 in TNBC has been reported to be associated with poor prognosis[9,12]. Therefore, targeting BAD phosphorylation at

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