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Atypical PKC signaling and breast cancer metastasis

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Triple-negative breast cancer (TNBC) is a distinct breast cancer subtype defined by the absence of estrogen receptor (ER), progesterone receptor (PR) and epidermal growth factor receptor 2 (HER2/neu), and the patients with TNBC are often diagnosed with higher rates of recurrence and metastasis. Because of the absence of ER, PR and HER2/neu expressions, TNBC patients are insensitive to HER2-directed and endocrine therapies available for breast cancer treatment. Here, we report that expression of atypical protein kinase C isoform, PKCλ/ι, significantly increased and activated in all invasive breast cancer (invasive ductal carcinoma or IDC) subtypes including the TNBC subtype. Because of the lack of targeted therapies for TNBC, we choose to study PKCλ/ι signaling as a potential therapeutic target for TNBC. Our observations indicated that PKCλ/ι signaling is highly active during breast cancer invasive progression, and metastatic breast cancers, the advanced stages of breast cancer disease that developed more frequently in TNBC patients, are also characterized with high levels of PKCλ/ι expression and activation. Functional analysis in experimental mouse models revealed that depletion of PKCλ/ι significantly reduces TNBC growth as well as lung metastatic colonization. Furthermore, we have identified a PKCλ/ι-regulated gene signature consisting of 110 genes, which are significantly associated with indolent to invasive progression of human breast cancer and poor prognosis. Mechanistically, cytokines such as TGFβ and IL1β could activate PKCλ/ι signaling in TNBC cells and depletion of PKCλ/ι impairs NF-κB p65 (RelA) nuclear localization. We observed that cytokine-PKCλ/ι-RelA signaling axis, at least in part, involved in modulating gene expression to regulate invasion of TNBC cells. Overall, our results indicate that induction and activation of PKCλ/ι promote TNBC growth, invasion and metastasis. Thus, targeting PKCλ/ι signaling could be a therapeutic option for breast cancer, including the TNBC subtype.

Biography

Paul has completed his PhD from Calcutta University and postdoctoral studies from University of Wisconsin School of Medicine and Public Health. He is an Associate Professor and the Director of the Garduate Program within the Department of Pathology & Laboratory Medicine at the University of Kansas Medical Center. He has published more than 30 papers in reputed journals and has been serving as an editorial board member of the journal Scientific Reports.

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