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PSMD12 promotes breast cancer growth via inhibiting the expression of pro-apoptotic genes

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ABSTRACT

Breast cancer (BC), the most frequent cancer in women worldwide, is extremely heterogeneous. For effective and precise treatment and to cope with drug resistance in BC, we need to find more therapeutic molecular targets. In this study, we found that the Proteasome 26S Subunit, Non-ATPase 12 (PSMD12) was upregulated in BC samples, its expression was heterogeneous among different cell lines, and high levels of *PSMD12* were related to poor prognosis of BC patients. Notably, the expression of PSMD12 increased in the nucleus. Cytological experiments revealed that *PSMD12* knockdown inhibited cell growth and migration, and a genome-wide CRISPR-Cas9 knockout (GeCKO) screen also confirmed that *PSMD12* is a crucial gene for the growth of BC cells. Flow cytometry showed that cell apoptosis increased in the *PSMD12* knockdown, and RNA-seq indicated that the apoptosis pathway was activated, and the *TXNIP*, *GADD45A*, *GADD45B*, *RHOB*, and *CDKN1A* pro-apoptotic genes were highly expressed, a result that was validated by RT-qPCR and Western blot. Furthermore, restoration of *PSMD12* expression decreased the expression of pro-apoptotic genes. A tumor-bearing mice assay demonstrated that BC growth was arrested by reduced PSMD12 levels *in vivo*. Taken together, PSMD12, a subunit of 19S regulator of 26S proteasome, was identified as a potential prognostic and therapeutic molecular target for BC, which provides a new insight for developing anticancer drugs that promote apoptosis based on the targeting of the 26S proteasome complex.

1. Introduction

Breast cancer (BC), which has the highest incidence (24.2%) and mortality (15.0%) among the ten most common cancers [1], is the most common gynecological cancer threatening women's health worldwide. In China, the incidence of BC ranks first (45.29/100,000), and the mortality rate ranks fifth (10.05/100,000) among women [2]. BC has substantial heterogeneity, and it is a life-threatening event that seriously affects women's physical and mental health [3–5]. Surgery, chemoradiotherapy, endocrine therapy, and immunotherapy can prolong the survival of patients, but some subtypes can evade these treatments by showing drug resistance, metastasis, and recurrence, leading to severe side effects [6–9]. Thus, the current existing targets are insufficient to meet the needs of individualized therapy. Given this context, developing more potential targets has profound significance for BC patients.

PSMD12 (Proteasome 26S Subunit, Non-ATPase 12, PSMD12) is a non-ATPase subunit of the 19S regulator of 26S proteasome complex that plays a critical role in regulating cell cycle, DNA damage repair, and apoptosis by keeping protein homeostasis through the removal of misfolded or damaged proteins [10–13]. Mutation of *PSMD12* was discovered in neurodevelopmental disorder with autistic features as well as fetus with craniofacial dysmorphism, equinovarus feet, and syndactyly [14,15]. *De novo* disruption assay also supported the biological importance of PSMD12 in the proteasome function, particularly during development and neurogenesis [10]. Although other components of proteasome 26S, such as PSMD1 [11], PSMD2 [16], and PSMD4 [17], were uncovered to regulate cell growth and chemosensitivity, the function of PSMD12

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