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Editorial

RPN2: A Promising Therapeutic Target for Breast Cancer?

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Editorial

Ribopholin II (RPN2) is a type I integral membrane protein localized to the rough endoplasmic reticulum [1]. RPN2 is partly involved in the N-lined glycosylation reaction that conjugates high mannose oligosaccharides to the asparagine residues found in the N-X-S/T consensus sequence of nascent polypeptide chains [2]. Changes in glycosylation patterns are common in both normal and abnormal biological processes, including cancer in which aberrant glycosylation is associated with malignant transformation and promotes the acquisition of invasiveness and metastatic ability [3–5].

N-linked glycosylation is modulated by an oligosaccharyl transferase (OST) complex comprising seven subunits: ribophorin I (RPN1), DAD1, N33/IAP, OST4, STT3A/STT3B, Ost48, and RPN2 [2]. RPN1 regulates the glycosylation of several glycoproteins by selectively interacting with, and delivering them to, the catalytic core of the OST complex [6,7]; however, the role of RPN2 is not well characterized. Honma et al. were the first to discover that RPN2 plays an important role in the acquisition of drug resistance by breast cancer cells [8]. They examined the responses of breast cancer patients to docetaxel and found that non-responders showed higher expression of RPN2 than responders [8,9]. In drug-resistant breast cancer, RPN2 modulates the N-linked glycosylation of p-glycoprotein (a major cause of docetaxel resistance), thereby regulating its efflux activity [8]. Since drug resistance is a major focus of current cancer research, targeting p-glycoprotein with small molecules, including natural products and peptides, is a promising approach to overcoming cancer recurrence and a subsequent poor prognosis. Therefore, silencing RPN2 with siRNAs might improve the outcome for drug-resistant breast cancer patients.

Our own group reported that RPN2 is highly expressed in a population of breast cancer stem cells (CSC) expressing the CD44high/CD24low antigen phenotype [10]. In addition, Mani et al. demonstrated that non-CSC acquires the CD44high/CD24low antigen phenotype after epithelial to mesenchymal transition (EMT), resulting in drug resistance and high tumorigenicity [11]; therefore, EMT regulators such as Snail, Slug, and Twist are important factors for CSC generation. RPN2 induces EMT and metastatic activity in highly metastatic breast cancer cells by stabilizing Snail [12]. It does this by inhibiting GSK3β, a serine/threonine protein kinase that normally suppresses Snail expression and destabilizes the Snail protein [12]. Interestingly, Zhu et al. found that RPN2 is also highly expressed in pancreatic CSCs [13].

A recent study shows that RPN2 is associated with the N-linked glycosylation of CD63 [14]. CD63 is a member of the tetraspanin super family [15] and a component of exosomes (small extracellular vesicles containing proteins and small RNAs) [16]. A number of studies report that, in addition to extracellular communication, exosomes play important roles in cancer development and metastasis [17,18]. As RPN2 is highly expressed in breast CSCs and regulates the localization of CD63 at the cell surface, it might be involved in the development of a pre-metastatic niche. Taken together, the results of the tudies discussed herein suggest that identifying the role of RPN2 in cancer biology may shed light on the mechanisms underlying CSC generation and lead to promising approaches to treating intractable cancers.

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