

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-linked 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 CD44<sup>high</sup>/CD24<sup>low</sup> antigen phenotype [10]. In addition, Mani et al. demonstrated that non-CSC acquires the CD44<sup>high</sup>/CD24<sup>low</sup> 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 GSK3 $\beta$ , 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 studies 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.

## References

1. Crimando C, Hortsch M, Gausepohl H, Meyer DI. Human ribophorins i and ii: The primary structure and membrane topology of two highly conserved rough endoplasmic reticulum-specific glycoproteins. *The EMBO journal*. 1987; 6: 75-82.
2. Kelleher DJ, Gilmore R. An evolving view of the eukaryotic oligosaccharyltransferase. *Glycobiology*. 2006; 16: 47R-62R.
3. Weng TY, Chiu WT, Liu HS, Cheng HC, Shen MR, Mount DB, et al. Glycosylation regulates the function and membrane localization of KCC4. *Biochim Biophys Acta*. 2013; 1833: 1133-1146.
4. Dai L, Liu Y, He J, Flack CG, Talsma CE, Crowley JG, et al. Differential profiling studies of n-linked glycoproteins in glioblastoma cancer stem cells upon treatment with gamma-secretase inhibitor. *Proteomics* 2011; 11: 4021-4028.
5. Contessa JN, Bhojani MS, Freeze HH, Ross BD, Rehemtulla A, Lawrence TS. Molecular imaging of n-linked glycosylation suggests glycan biosynthesis is a novel target for cancer therapy. *Clinical cancer research: an official journal of the American Association for Cancer Research*. 2010; 16: 3205-3214.
6. Qin SY, Hu D, Matsumoto K, Takeda K, Matsumoto N, Yamaguchi Y, et al. Malectin forms a complex with ribophorin I for enhanced association with misfolded glycoproteins. *J Biol Chem*. 2012; 287: 38080-38089.
7. Wilson CM, High S. Ribophorin I acts as a substrate-specific facilitator of N-glycosylation. *J Cell Sci*. 2007; 120: 648-657.
8. Honma K, Iwao-Koizumi K, Takeshita F, Yamamoto Y, Yoshida T, Nishio K, et al. RPN2 gene confers docetaxel resistance in breast cancer. *Nat Med*. 2008; 14: 939-948.
9. Iwao-Koizumi K, Matoba R, Ueno N, Kim SJ, Ando A, Miyoshi Y, et al. Prediction of docetaxel response in human breast cancer by gene expression profiling. *J Clin Oncol*. 2005; 23: 422-431.
10. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. *Proc Natl Acad Sci U S A*. 2003; 100: 3983-3988.
11. Mani SA, Guo W, Liao MJ, Eaton EN, Ayyanan A, Zhou AY, et al. The epithelial-mesenchymal transition generates cells with properties of stem cells. *Cell*. 2008; 133: 704-715.

12. Takahashi RU, Takeshita F, Honma K, Ono M, Kato K, Ochiya T. Ribophorin II regulates breast tumor initiation and metastasis through the functional suppression of GSK3 $\beta$ . *Sci Rep*. 2013; 3: 2474.
13. Zhu J, He J, Liu Y, Simeone DM, Lubman DM. Identification of glycoprotein markers for pancreatic cancer CD24+CD44+ stem-like cells using nano-LC-MS/MS and tissue microarray. *J Proteome Res*. 2012; 11: 2272-2281.
14. Tominaga N, Hagiwara K, Kosaka N, Honma K, Nakagama H, Ochiya T. RPN2-mediated glycosylation of tetraspanin CD63 regulates breast cancer cell malignancy. *Mol Cancer*. 2014; 13: 134.
15. Pols MS, Klumperman J. Trafficking and function of the tetraspanin CD63. *Exp Cell Res*. 2009; 315: 1584-1592.
16. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol*. 2007; 9: 654-659.
17. Zhou W, Fong MY, Min Y, Somlo G, Liu L, Palomares MR, et al. Cancer-secreted miR-105 destroys vascular endothelial barriers to promote metastasis. *Cancer Cell*. 2014; 25: 501-515.
18. Wang T, Gilkes DM, Takano N, Xiang L, Luo W, Bishop CJ, et al. Hypoxia-inducible factors and rab22a mediate formation of microvesicles that stimulate breast cancer invasion and metastasis. *Proceedings of the National Academy of Sciences of the United States of America* 2014; 111: E3234-3242.