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COMMENTARY

Invited Commentary: Role of Estrogen Receptor-α in Regulating Claudin-6 Expression in Breast Cancer Cells

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Tight junctions (TJs) contribute to the paracellular barrier, which is a fence that divides plasma membranes and signal transduction, acting as a multifunctional complex in vertebrate epithelial and endothelial cells [1]. The morphological features of TJs fits well with their functions. The TJ core is a fibril-like proteinaceous structure within the lipid bilayer, the so-called TJ strands [2]. Identification and characterization of TJs-associated proteins during the last two decades has unveiled the nature of TJ strands and how they are spatially organized. The interplay between integral membrane proteins, claudins, and cytoplasmic plaque proteins, ZO-1/ZO-2, is critical for TJ formation and function [3].

Among the TJ-associated proteins, the claudin family of membrane proteins, identified in 1998 by the Tsukita group, are key molecules in the architecture and barrier function of TJs [4]. Claudins maintain cell polarity and are involved in recruiting signaling proteins. Claudins are also hypothesized to be involved in the regulation of proliferation, differentiation, and other cellular functions [5].

TJ dysfunction has been presumed as a mechanism for the loss of cell adhesion and an important step in the progression of cancer to metastasis. Because claudin expression patterns are tissue- and cell-specific, recent studies have suggested that claudins might be useful molecular markers for many different cancers [6,7]. Moreover, claudins are a potential target for novel antibody-based therapies of diverse cancers [8].

Until now, 24 members of the claudin family have been identified. The role of claudins in breast cancer is unknown and not well-explored, but recent reports have shown that claudins 3 and 4 are overexpressed in breast cancer, whereas claudins 1 and 7 are downregulated or completely absent [9-11]. Furthermore, Szasz et al. [12] indicated that the loss of claudins might contribute to breast cancer progression, and that certain claudin expression patterns might be of prognostic relevance. These results suggest that claudin subtypes may have different roles during different stages of breast cancer.

Claudin-6 is expressed during the early stage of epidermal morphogenesis and is crucial to epidermal differentiation and barrier formation [13]. A recent report showed that claudin-6 is preferentially expressed in mammary epithelial cells and functions as a breast cancer tumor suppressor [14]. Additionally, Osanai et al. [15] suggested that the claudin-6 methylator phenotype might contribute to enhance tumorigenic and invasive properties of breast cancer cells. However, no information is available on the regulating mechanism of claudin-6 expression in breast cancer. In this study by Yafang et al. [16], authors demonstrated that estrogen induces claudin-6 expression through an estrogen receptor (ER) α pathway in MCF-7 cells. The data are clear, and this is the first report showing that claudin-6 expression was associated with ERα in breast cancer cells. However, first of all, authors had to indicate how claudin-6 expression is related to ERs. It was necessary to study claudin-6 expression in ER (+) and ER (-) breast cancer (prior to ERα and ERβ cells). Authors described in their previous studies that no significant association was found between claudin-6 expression and ER (+) breast cancer (even ERs). It is well accepted that the MCF-7 cell line may vary depending on *in vitro* culture conditions. Therefore, disparate results may occur during *in vitro* selection conditions. Although results from a laboratory setting may not exactly correlate with *in vivo* results, there is little significance to a research finding that only has significance *in vitro*. Because claudin-6 expression was also observed in ERβ (+) breast cancer cells, authors must show that claudin-6 is expressed in the MDA-MB-231 cancer cell line and demonstrate that the ERβ pathway is not associated with this protein

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expression. But this was also omitted. Thus, further investigation with a much larger cohort should be performed to confirm the relationship between claudin-6 and ERs.

Claudin expression is associated with breast cancer prognosis. Down-regulation of claudin-2 is significantly associated with lymph node metastasis and high clinical stage [17]. Additionally, high levels of claudin-4 are associated with adverse outcomes in patients with breast cancer [18]. Therefore, it is also necessary to evaluate the clinicopathological parameters of breast cancers to determine whether claudin-6 could be used as a predictor of survival or prognosis.

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