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Role of Lactoferrin in the Carcinogenesis of Triple-Negative Breast Cancer

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Editorial

Lactoferrin is a ubiquitous, secretory, iron binding glycoprotein found in exocrine secretions such as saliva, pancreatic secretions and bile of mammals, including humans. It is considered a member of the transferrin family due to a close resemblance in molecular structure and size. Lactoferrin is produced in neutrophils and stored in specific granules. Its secretion from polymorphonuclear cells into circulation is dependent on the activation of guanylate cyclase, cGMP and protein kinase C. Lactoferrin gene expression is modulated by the steroid-thyroid receptor superfamily, indicating that it is a hormone responsive gene. Lactoferrin is reported to have a variety of biological functions, including DNA synthesis, immune responses, iron transport, antimicrobial action, RNase activity, transcriptional activating functions, and receptor-mediated lipid uptake, any of which could play a role in tumor promotion [1-12]. Being a hormone responsive gene, lactoferrin may contribute to various hormone dependent cancers such as breast cancer and cancers of the female reproductive tract. In this context, it is important to note that an earlier report has shown an inverse relationship with the level of estrogen receptor and lactoferrin [13,14]. It was also found that lactoferrin and steroid hormone receptor expression are down regulated in adenocarcinomas of the endocervix, which may be associated with the loss of differentiation during neoplastic transformation [14]. Lactoferrin expression, similar to endocervix, is highly expressed in women's normal resting and lactating breasts, but seems to be progressively downregulated in many breast cancers.

Recently, it was also postulated that elevated levels of lactoferrin are associated with reduced expression of ERα and PR, and perhaps HER-2, and therefore could contribute to the development of triple negative breast cancer (TNBC) phenotypes [15]. It was found that lactoferrin efficiently downregulates ERα, PR, and HER-2, and the increased invasiveness and aggression of these breast cancer cell lines was attributed to the lactoferrin-endothelin axis.

Based on the several experiments by Ha et al. [15], it was found that persistant exposure of breast cancer cells to lactoferrin resulted in downregulation of the hormone receptors leading to the development of TNBC phenotypes. This increase in lactoferrin was accompanied by an increase in the levels of cyclin-D which indicates cell cycle progression. It was also validated that lactoferrin uses post-transcriptional mechanisms sensitive to proteosomal degradation of proteins in order to downregulate the hormonal receptors. Tamoxifen blocked estrogen-mediated cell migration and invasiveness in ER+ cell lines. Herceptin (transtuzumab) has a similar effect on Her-2 cell lines as well. However, it was found that lactoferrin-treated cells have decreased responsiveness to both the drugs [15]. Most importantly, it was found that lactoferrin regulates the expression of endothelin 1 (ET-1) [15], shown by the presence of three lactoferrin-motifs in the ET-1 promoter region. ET-1 exerts its biologic effects via an autocrine and/or paracrine manner through specific receptors, and supports tumor cell proliferation, invasion, angiogenesis and neovascularization [16-22].

A contrary study showed that treatment of human breast cancer cell lines with bovine Apo-lactoferrin increases apoptosis and decreases cell migration [23]. But bovine lactoferrin does not bind to the endothelin 1 promoter region. Hence, ET-1 is a lactoferrin-inducible gene and only the holo form of lactoferrin is responsible for the downregulation, as well as increased invasiveness, in breast cancer cells. It was also found that the levels of lactoferrin and ET-1 were increased in TNBC specimens as compared to those in the control ER +/PR+ breast tumors [15].

The advent of targeted pharmacotherapy and immunotherapy for the management of different kinds of cancers has opened up new avenues for attacking cancer cells at the molecular level, thus offering the potential to manage the most aggressive tumors effectively. The use of ET-1 receptor blockers to antagonize the effects of ET-1 on tumor cells has undergone preclinical and clinical testing [24]. Identifying the involvement of lactoferrin-endothelin axis in triple negative breast cancer opens the door to various therapeutic solutions to these aggressive and invasive cancers.

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