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Resistin Facilitates Breast Cancer Progression via TLR4-Mediated Induction of Mesenchymal Phenotypes and Stemness Properties

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Growing evidence indicates that resistin—an obesity-related cytokine—is upregulated in breast cancer patients, yet its impact on breast cancer behavior remains to be ascertained. Similarly, Toll-like receptor 4 (TLR4) has been implicated in breast cancer progression, however, its clinically relevant endogenous ligand remains elusive. In this study, we observed that high serum resistin levels in breast cancer patients positively correlated with tumor stage, size and lymph node metastasis. These findings were replicated in animal models of breast cancer tumorigenesis and metastasis. Resistin was found to promote epithelial–mesenchymal transition and stemness in breast cancer cells—mechanisms critical to tumorigenesis and metastasis—through a TLR4/nuclear factor kappa-light-chainenhancer of activated B cells (NF-κB)/signal transducer and activator of transcription 3 (STAT3) signaling pathway and negated by TLR4-specific antibody and antagonist. These findings provide clear evidence that resistin is a clinically relevant endogenous ligand for TLR4, which promotes tumor progression via TLR4/NF-κB/STAT3 signaling, providing insights into a novel therapeutic target in breast cancer.

Key words: Resistin, breast cancer, TLR4, mesenchymal, stemness