Paracrine-acting adiponectin promotes mammary epithelial differentiation and synergizes with genistein to enhance transcriptional response to estrogen receptor β signaling.


Source

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Abstract

Mammary stromal adipocytes constitute an active site for the synthesis of the adipokine, adiponectin (APN) that may influence the mammary epithelial microenvironment. The relationship between "local," mammary tissue-derived APN and breast cancer risk is poorly understood. Here, we identify a novel mechanism of APN-mediated signaling that influences mammary epithelial cell proliferation, differentiation, and apoptosis to modify breast cancer risk. We demonstrate that early dietary exposure to soy protein isolate induced mammary tissue APN production without corresponding effects on systemic APN levels. In estrogen receptor (ER)-negative MCF-10A cells, recombinant APN promoted lobuloalveolar differentiation by inhibiting oncogenic signal transducer and activator of transcription 3 activity. In ER-positive HC11 cells, recombinant APN increased ERβ expression, inhibited cell proliferation, and induced apoptosis. Using the estrogen-responsive 4X-estrogen response element promoter-reporter construct to assess ER transactivation and small interfering RNA targeting of ERα and ERβ, we show that APN synergized with the soy phytoestrogen genistein to promote ERβ signaling in the presence of estrogen (17β-estradiol) and ERβ-specific agonist 2,3-bis(4-hydroxyphenyl)-propionitrile and to oppose ERα signaling in the presence of the ERα-specific agonist 4,4',4''-(4-propyl-(1H)-pyrazole-1,3,5-triy)trisphenol. The enhancement of ERβ signaling with APN + genistein cotreatments was associated with induction of apoptosis, increased expression of proapoptotic/prodifferentiation genes (Bad, p53, and Pten), and decreased antiapoptotic (Bcl2 and survivin) transcript levels. Our results suggest that mammary-derived APN can influence adjacent epithelial function by ER-dependent and ER-independent mechanisms that are consistent with reduction of breast cancer risk and suggest local APN induction by dietary factors as a targeted approach for promotion of breast health.