Role of TGFβ in the Anti-Estrogen Response/Resistance of Human Breast Cancer

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Transforming growth factor β (TGFβ) has potent inhibitory effects upon epithelial proliferation and malignant progression may be associated with breakdown of the autocrine and paracrine inhibitory loops in which TGFβ participates. The therapeutic effects of anti-estrogens may be partially attributable to boosting of local endogenous levels of TGFβ. This article reviews the evidence in support of TGFβ being a proximate effector in mediation of the anti-neoplastic effects of anti-estrogens. Both the conventional estrogen receptor (ER) dependent and ER independent mechanisms of action are likely to be involved. Evidence for preferential stromal induction of TGFβ by anti-estrogens is emphasized, together with the therapeutic potential of this strategy for improving outcome in early breast cancer irrespective of ER status.

KEY WORDS: Anti-estrogens; breast cancer; TGFβ; autocrine; paracrine.

INTRODUCTION

Anti-estrogens are the most widely used agents for the treatment of early and advanced breast cancer in both pre- and postmenopausal women, and their prophylactic application is under investigation. The original group of anti-estrogens were triphenylethylene derivatives of which tamoxifen is the dominant member and clinical prototype. Other agents within this group have relatively restricted clinical use at present and include toremifene, droloxifene, and idoxofene. Like tamoxifen, these each have in common a triphenylbutene core and a basic/polar side chain. This fundamental structure imparts a complex functional profile to this group of compounds which behave as "impure" anti-estrogens with mixed agonist/antagonist properties at the level of interaction with the estrogen receptor (ER). Thus in addition to acting as a competitive inhibitor for the ligand binding site of the ER blocking expression of certain estrogen regulated genes, these "impure" anti-estrogens permit dimerization of the ER and binding of the ligand/ER complex to the estrogen response element (ERE). Hence, binding of these anti-estrogens results in an attenuated transcriptional response with expression of some genes which would otherwise be stimulated by binding of natural hormonal ligands (1) (Fig. 1). These intrinsic agonist properties may ultimately compromise the anti-tumor efficacy of these agents, and the newer "pure" anti-estrogens which act exclusively as antagonists may offer clinical advantages (2).

Though much experimental and clinical data testifies to anti-estrogens mediating their effects principally via the ER, compelling evidence has accrued for operation of ER-independent mechanisms of action (3). These effects may be relatively more important for "impure" compared with "pure" anti-estrogens, but they are not confined to compounds with a triphenylbutene core. Nevertheless, this basic structure may be partly responsible for the functional pleiotropy of impure anti-estrogens since its unique chemical struc-
Fig. 1. In ER-positive cells, anti-estrogens act as competitive antagonists for the ligand binding site of the ER (Fig. 1A). "Pure" anti-estrogens completely block transcription of estrogen-regulated genes, but "impure" anti-estrogens permit a partial transcriptional response driven by a constitutively active TAF-1. In ER-negative cells, ER-independent mechanisms for controlling transcription of estrogen responsive genes may be operative (Fig. 1B).

The local micro-environment of tumor cells contains a pool of both positive and negative growth factors functioning in either an autocrine or paracrine manner to effect estrogen mediated tumor progression (9). Moreover, hormone-dependent breast cancer could become hormone-independent by the constitutive expression of these same growth factors, thereby acquiring autonomy.

In accordance with the extended autocrine hypothesis (10), cells which have lost an inhibitory response would have a selective growth advantage, and estrogen stimulation could result from a simultaneous increase in levels of growth stimulators and decrease of growth inhibitors. TGFβ is the principle negative growth modulator in mammalian tissues with potent inhibitory effects upon a range of epithelial (11, 12) and endothelial cell types (13), including breast cancer cells in vitro (12, 14). Conversely, TGFβ is generally stimulatory to cells of mesenchymal origin, such as fibroblasts (15). It is the former property which has attracted interest in these factors as important negative regulators of epithelial proliferation in both normal and malignant tissue. Because receptors for TGFβ are