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Review

Reappraisal of the Concept of Hormone Therapy in Metastatic Prostate Cancer and Implications for Treatment☆

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Abstract

Almost all prostate cancer patients become resistant to hormonal therapy that blocks androgen-mediated cell proliferation. The key to this resistance may lie in expression of the androgen receptor itself. Alternative methods to block the AR-mediated signaling pathways appear to be critical for tumor survival. These signal transduction pathways that interact with AR may enhance the response to androgen ablation therapy. The identification of signaling pathways may be a major goal in the treatment of prostate cancer. The application of novel therapies must be preceded by the identification of the genetic and molecular tumor profiles for each patient.

Keywords: Androgen receptor; Signal transduction pathways; Novel therapy

1. Introduction

In metastatic prostate cancer, nearly all treated patients become resistant to hormone therapy blocking androgen-mediated tumor proliferation. Recent analysis of the gene expression profile and the signaling pathways involved in androgen-independent tumor growth shows that resistance to hormone therapy may be related to overexpression of the androgen receptor (AR) or to signal transduction pathways interacting or not with AR [1,2]. In these very heterogeneous, hormone-resistant prostate cancers, an understanding of the mechanisms regulating hormone resistance suggests new treatment strategies.

2. Hormone therapy: conventional view

Since the work of Huggins in 1940, first-line therapy of hormone-sensitive metastatic prostate cancer is based on androgen suppression: LH-RH agonists, non-steroidal antiandrogens, orchidectomy or a combination of both. Oral estrogens were initially used to suppress the secretion of androgens and gave a response rate better than orchidectomy or equivalent to a complete androgen block. Oral estrogens obtain and maintain castration levels of testosterone and have a direct cytotoxic effect on prostate cells. However, they have been abandoned because of the risk of cardiovascular side effects even with doses as low as one mg.

Hormone therapy has remained the therapy of first choice up until now as 80% of bone metastases are hormone-sensitive. However its efficacy is limited [3]:

- it does not improve patient survival even if its early administration reduces bone morbidity,
- prolonged androgen suppression has harmful effects on the bone (bone loss),
- evolution towards resistance to hormone therapy is irreversible [4,5].

3. The concept of androgen independence

In prostate cancer, AR stimulates the growth of malignant cells in an autocrine manner through survival and growth factors [6]. The reduction in levels of circulating androgens inhibits tumor proliferation and

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induces apoptosis of tumor cells [7]. Hormone treatment leads to the development of a state refractory to the suppressive action of hormone therapy called hormone refractory or hormone-resistant state. Nevertheless, AR continues to be expressed in most hormone-resistant prostate cancers suggesting that it remains functional for the growth and the survival of tumor cells [8]. Several mechanisms are involved in hormone resistance [9–11]

- genetic changes following mutations or amplification of the AR gene which occur in less than 10% of the patients [12–15],
- interaction of AR with the other signaling transduction pathways [16],
- increase in ligand-dependent expression of AR,
- other AR independent mechanisms.

3.1. Genetic modifications

A subgroup of mutations appears in the field of ligand binding and modifies the response of AR to estrogens, hydrocortisone and to receptor antagonists such as flutamide which then behave like agonists [16].

3.2. Interaction of AR with HER-2-dependent signaling pathways

HER-2 (Human Epidermal Receptor-2) is a member of the EGF receptor family (Epidermal Growth Factor) and mainly functions as a co-receptor. The expression of HER-2 by tumor cells is associated with progression towards hormone resistance and decreases the activity of AR antagonists [17]. HER-2 activates the transcription of AR in the absence of androgens and has a synergic action with low levels of androgens to activate this transcription pathway. HER-2 may promote growth and survival of androgen-independent tumor cells by two signal transduction pathways: the PI3K/Akt pathway [18] and the MAP kinase pathway (MAPK) [19,20] which activate AR independently from its ligand [21] (Fig. 1). Antiandrogens do not block the HER-2 route.

The chaperon molecule Hsp 90 (Hot shock protein) plays an important role by regulating the function and stability of a large number of proteins on which tumor cells depend to survive. Vanaja et al. [22] showed that Hsp 90 ensures the stability of AR in prostate cancer cells and regulates the affinity of AR for its ligand [23]. Levels of AR are reduced by an Hsp 90 inhibitor, geldanamycin (GA) which preferentially destabilizes the AR bound to antiandrogens the efficacy of which may be increased by combination with an Hsp 90 inhibitor. GA also prevents the nuclear translocation of AR bound to its ligand and its transcription. A GA

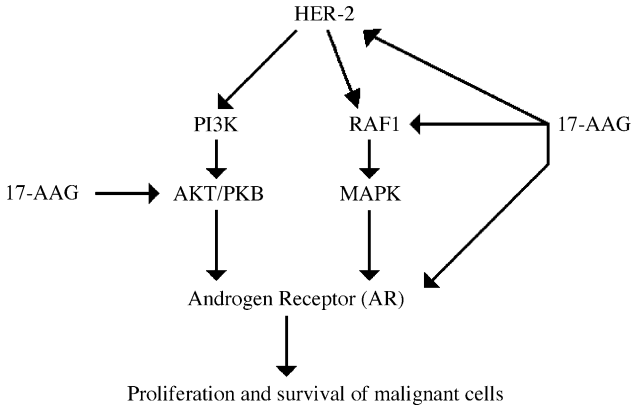

Fig. 1. HER-2-dependent signalling pathways in androgenoindependent prostate cancer. PI3K: Phosphatylinasitol 3-kinase. MAPK: Mitogen Activated Protein Kise.

derivative, 17-AAC (17-Allylamino-17-demethoxygeldanamycin) induces the breakdown of AR, HER-2 and Akt in prostate cancer xenografts thereby inhibiting their growth [24]. Akt and HER-2 are ‘‘client’’ proteins of Hsp 90 (that is, proteins which also depend on Hsp 90 for their stability). Hsp 90, depending on its conformation, recruits cochaperons to assemble distinct complexes: one complex promoting the breakdown of ‘‘client’’ proteins by the proteosome and another complex promoting the stabilization of Hsp 90 ‘‘client’’ proteins. By binding to Hsp 90, 17-AAC leads to the accumulation of the complex degraded by the proteosome with the concomitant loss of the stabilizing complex [25].

Degradation of HER-2 and Akt is ensured by 17-AAC and GA [26,27]. That of Raf-1 by 17-AAC and GA prevents the activation of the MAPK pathway by growth factors or cytokines (Fig. 1). 17-AAG has a potent anti-tumor activity in breast cancer xenografts overexpressing HER-2. In these models, the overexpression of HER-2 has been associated with a poor prognosis and resistance to chemotherapy notably with paclitaxel. The overexpression of HER-2 increases the sensitivity of tumor cells to Hps 90 inhibitors. Anti HER-2 antibody (trastuzumab) and 17-AAG increase the survival of tumor xenografts in the mouse. In prostate cancer, the overexpression of HER-2 inhibits p34cd2 the activation of which is necessary for paclitaxel-induced apoptosis. Anti HER-2 antibody (trastuzumab) and paclitaxel already used in metastatic breast cancer may be combined with 17-AAG and with paclitaxel in metastatic prostate cancer.

Solit et al. [24] also showed that 17-AAG provokes the breakdown of the wild and mutated form of AR in vitro and in vivo. The fact that AR remains sensitive to 17-AAC suggests that AR mutations which allow it to