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Review article

The androgen receptor for the radiation oncologist

Récepteur aux androgènes : ce que l'oncologue radiothérapeute doit savoir

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ABSTRACT

Androgen deprivation therapy is widely used in combination with radiotherapy for the treatment of prostate cancer. The knowledge of the biology of the androgen axis could help the radiation oncologist to combine both modalities in an efficient way. Moreover, new drugs have recently been approved and their role in combination with radiation needs pre-clinical and clinical studies. This review summarized the main data on the biology of androgen receptor and the potential implications for the physician. Mechanisms of interactions between androgen deprivation therapy and radiotherapy are also presented and discussed.

Mots clés :
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RÉSUMÉ

La suppression androgénique est de plus en plus utilisée en association avec la radiothérapie dans le cancer de prostate. La connaissance de la biologie des androgènes peut aider l'oncologue radiothérapeute dans le maniement des associations d'hormonothérapie et de radiothérapie. En outre, de nouveaux médicaments ont été récemment mis sur le marché dans le cadre du cancer de prostate résistant à la castration. Leur emploi potentiel avec la radiothérapie doit être évalué dans le cadre d'études précliniques et cliniques. Cette revue résume les connaissances acquises sur le récepteur aux androgènes et leurs implications potentielles pour le clinicien. Les mécanismes d'interaction entre la suppression androgénique et la radiothérapie sont également résumés.

1. Introduction

Combination of androgen deprivation therapy and radiotherapy is now the standard of care for prostate cancers patients of the high-risk group and some of the intermediate group. If the clinical benefit of this association is now clearly demonstrated, the biological interactions between the hormonal treatment and radiotherapy are not fully understood. Moreover, new hormonal agents as abiraterone and enzalutamide have been approved for the treatment of castration-resistant prostate cancers. Their use in earlier phases of the disease, particularly with radiotherapy, is more and more discussed.

The aim of this review is to summarize the present knowledge of the physiology of the androgen receptor and to discuss the potential interactions between old and new hormonal drugs with radiation.

2. Prostate cancer and androgens

2.1. Prostate cancer biology

Prostate is a gland that synthesizes components of the seminal fluid, including proteases as prostate-specific antigen (PSA). In the normal adult prostate, the androgen receptor is expressed in all luminal cells and in some epithelial basal cells as well in stromal cells.

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Prostate cancer develops from epithelial cells, but it is not clear if it arises from basal or luminal cells [1]. However, the role of stromal cells is essential to promote growth of prostate cancer, through the secretion of various growth factors. More than 50% of prostate cancers harbour a gene fusion between the promoter of transmembrane protease, serine 2 (TMPRSS2) and portions of the coding regions of E-twenty-six (ETS) transcription factors [2], mainly erythroblast transformation-specific gene (ERG). TMPRSS2 is an androgen responsive gene (see below). The ETS family members are transcription factors, regulating cell proliferation, cell migration, cell cycle control and apoptosis [3]. Genomic profiling revealed that mutations in the androgen receptor signalling pathway is much more altered than the others pathways [4].

2.2. Androgen dependency of prostate cancer

Androgen stimulation is fundamental for prostate cancer growth. Androgen deprivation therapy has demonstrated more than 60 years ago a dramatic effect on cancer progression [5]. Androgen deprivation therapy is obtained by surgical castration or by the use of luteinizing hormone-releasing hormone (LH-RH) agonists or antagonists. Androgen deprivation therapy is supposed to reduce the serum testosterone level under 0.5 ng/mL. It is still debated whether a level lower than 0.2 ng/ml improves the clinical response rate and its duration. Combination of LH-RH agonists and anti-androgens is called complete androgen blockade: its usefulness was not demonstrated in the treatment of metastatic prostate cancer. The androgen receptor could induce directly cancer growth, for example via the TMPRSS2-ETS fusion factor. But it can also cross talks with numerous growth factors (transforming growth factor [βTGFβ], vascular endothelial growth factor [VEGF], insulin-like growth factor [IGF], epithelial growth factor [EGF] and fibroblast growth factor [FGF]). For instance, TGFβ cooperates with androgen receptor signalling to promote stromal cell growth. Androgen deprivation therapy remains the principal treatment of relapse after radiotherapy [6].

2.3. Androgens synthesis

Testosterone is the principal circulating androgen and is synthesized by the testis for the major portion. Less than 3% of the circulating testosterone is bioavailable, most of it being bound to different proteins, sex hormone-binding protein (SHBG) and albumin, essentially. The remaining androgens in the bloodstream (5–10%) are dehydroepiandrosterone (DHEA), androstenediol and androstenedione: they are produced by adrenals or by peripheral conversion of testosterone. Androgens production is regulated by the hypothalamic-pituitary-gonadal axis. LH-RH is secreted by the hypothalamus in pulses, thus stimulating luteinizing hormone (LH) secretion, which acts on Leydig cells in the testis to induce androgen production. Testosterone acts on hypothalamus through a negative feedback to prevent LHRH release.

Steroids synthesis begins with mobilization by the steroidogenic acute regulatory protein (StAR) and cleavage by CYP11A1 of cholesterol in pregnenolone (Fig. 1). Subsequent metabolism to mineralocorticoids, glucocorticoids, androgens or oestrogens depends of the enzymatic equipment of the tissue. Androgens are produced from the conversion of pregnenolone-like steroids by the CYP17, a cytochrome P450 enzyme. CYP17 catalyzes hydroxylase and lyase reactions: the hydroxylase activity is similar for pregnenolone and progesterone but the lyase activity is much more potent for 17-OH-pregenolone than 17-OH-progesterone. Hence, the synthesis of androgens is mainly performed via DHEA. Polymorphisms of the *CYP17* gene have been associated with a higher risk of prostate cancer and a worst prognosis of castration-resistant prostate cancers [7,8].

DHEA and androstenedione, synthesised in adrenal glands, are transformed in testosterone in the Leydig cells of the testis. Testosterone is released in the bloodstream and enters into the target cell via passive diffusion through the plasma membrane, but active transport by organic anion-transport polypeptides have been described [9]. Testosterone is converted into target tissues (prostate and a limited number of other tissues) in 5α-dihydro-testosterone by 5-alpha reductase (SRD5A1 or 2). There are two types of 5-alpha reductase, depending on the target tissue, the type 2 being more specific for prostatic epithelial cells.

3. The androgen receptor

The androgen receptor is a nuclear transcription factor and is a member of the steroid receptor superfamily. The androgen receptor gene is located on the X-chromosome at position Xq11-12 and contains eight exons that encode a protein of ≈919 amino acids. Two isoforms of androgen receptor have been described: the predominant isoform B (110 kDa) and the less dominant isoform A (80 kDa).

Like other members of the nuclear receptor superfamily, the androgen receptor is composed of four domains (Fig. 2) [10]:

- the transcriptional activation domain (exon 1: N-terminal domain): this domain is necessary and sufficient for transcription activity. It harbours a variable number of highly repetitive DNA sequences, such as CAG, coding for polyglutamin. The number of CAG repeats is correlated to the transcriptional activity of the androgen receptor, the shorter CAG repeat length resulting in a higher transcriptional activity. Racial groups with a high prevalence of prostate cancer had also more frequently a short CAG repeats, suggesting that early tumorigenesis is dependent on a more active androgen receptor. The N-terminal domain contains also coregulators' interaction domains;
- the DNA-binding domain (exon 2 and 3) with two zinc-finger regions;
- a flexible hinge region separates the DNA-binding domain from the androgen-binding domain: it contains the nuclear localization signal, allowing the androgen receptor to interact with the cytoskeleton and to migrate to the nucleus, after binding of importin-α [11];
- the ligand-binding domain at the C-terminal end (exons 4-8), containing an androgen-binding pocket.

The activation function AF-1 and AF-2 domains are required for optimal transactivation. AF-1 undergoes folding when contacted by transcription factor TFIIF after binding of the AR on DNA, enabling coregulators recruitment. AF2 is a coactivator-binding site, unmasked after ligand binding.

Ligand-free androgen receptor is sequestered in the cytoplasm bound to heat-shock proteins (HSP 70, 90 and p23), which protect it from degradation. After binding of the ligand, a conformational change of the androgen receptor occurs, which allows dissociation of heat-shock proteins.

Testosterone and dihydrotestosterone can bind to the androgen receptor, but the latter forms a more stable complex and is 3–10 times more potent. Binding of the ligand initiates an intramolecular interaction between the N-terminal domain and ligand-binding domain, termed N/C interaction [12]. The androgen receptor becomes phosphorylated and translocates into the nucleus (Fig. 3). The androgen receptor is phosphorylated at several sites by different kinases, including mitogen-activated protein kinase (MAPK), protein kinase C (PKC) and protein kinase B (AKT/PKB). They interact with the androgen receptor, usually in a ligand-dependent manner. Phosphorylation stabilizes the