

Spironolactone and XPB

Subjects: Biology

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Spironolactone (SP) is commonly used for the treatment of heart failure, hypertension, and complications of cirrhosis by antagonizing the mineralocorticoid receptor. However, SP also antagonizes the androgen receptor, and thus SP has also been shown to be effective in the treatment of acne, hair loss, and hirsutism in women. Interestingly, recent drug repurposing screens have identified new and diverse functions for SP as a simulator of tumor immunosurveillance and as an inhibitor of DNA repair and viral infection. These novel pharmacological effects of SP have all been linked to the ability of SP to induce the rapid proteolytic degradation of the xeroderma pigmentosum group B (XPB) protein. XPB is a critical enzymatic component of the multi-subunit complex known as transcription factor II-H (TFIIH), which plays essential roles in both DNA repair and the initiation of transcription. Given the critical functions for XPB and TFIIH in these processes, the loss of XPB by SP could lead to mutagenesis. However, the ability of SP to promote cancer stem cell death and facilitate immune recognition may counteract the negative consequences of SP to mitigate carcinogenic risk. Thus, SP appears to have new and interesting pharmacological effects that may extend its potential uses.

Keywords: DNA repair ; UV radiation ; genomic instability ; transcription ; tumor immunobiology ; drug screening ; mutagenesis ; DNA damage response ; viruses ; proteolysis

1. Introduction

The ideal small molecule compound exhibits specificity to a single enzyme or molecular entity to allow for maximum drug efficacy with minimal side effects. However, most pharmacological agents affect multiple biological targets, which can frequently limit the maximum tolerable dose or prevent the continued use of a drug. In some cases, the lack of specificity increases the number of disease states for which a given compound can be clinically employed. Spironolactone (SP) provides a classic example. First used in the treatment of hypertension and heart failure due to its ability to antagonize aldosterone action on the mineralocorticoid/aldosterone receptor, SP was later shown to also target the androgen receptor (Figure 1). This then led to the use of SP in a variety of androgen-induced dermatologic conditions, including acne vulgaris and the excessive hair growth condition hirsutism. Thus, a single agent can be prescribed to treat diverse disorders and disease states.

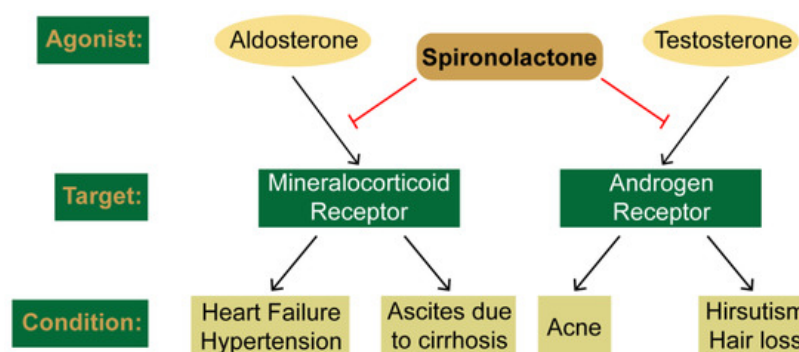


Figure 1. Traditional targets of spironolactone. Spironolactone antagonizes the actions of the aldosterone and testosterone towards their target receptors, the mineralocorticoid and androgen receptors, respectively. Inhibition of these receptors is used to treat the indicated conditions.

To capitalize on this lack of drug specificity and to lower the cost of drug therapies, drug repurposing screens are commonly carried out to identify new uses for old drugs ^[1]. SP again provides a pertinent example. As described in detail below, recent cell-based screens have identified diverse roles for SP in tumor immunotherapy ^[2], as adjuvants in DNA damage-based cancer chemotherapy ^{[3][4]}, and preventing viral infection ^[5]. Interestingly, as will be described below, these novel functions all appear to be associated with the ability of SP to induce the rapid proteolytic degradation of the

xeroderma pigmentosum group B (XPB) protein. XPB plays important roles in transcription and DNA repair, and thus the loss of these functions may cause SP to increase mutagenesis and cell death.

2. Clinical Uses and Canonical Targets of Spironolactone

2.1. SP as a Mineralocorticoid Receptor Antagonist

The mineralocorticoid aldosterone is secreted by the adrenal glands and is thought to contribute to a number of pathological conditions, including myocardial fibrosis, endothelial dysfunction, and vascular inflammation. These processes are involved in the development of heart failure, which is a leading cause of morbidity and mortality throughout the world. In the late 1950s and early 1960s, animal and human studies demonstrated that the synthetic mineralocorticoid SP could antagonize the renal excretory effects of aldosterone [8][7] and reduce arterial pressure in patients with hypertension [8][9]. Due to mineralocorticoid receptor (MR) antagonism in the kidney, SP results in increased excretion of sodium and water to lower fluid retention and lessen pressure on the heart. Both SP and the related mineralocorticoid antagonist (MRA) eplerenone (Figure 2) have been shown to reduce total and cardiovascular mortality in heart failure patients when administered along with other inhibitors of the renin–angiotensin–aldosterone (RAAS) system [10][11]. Canrenone, a metabolite of SP (Figure 2), also acts as an MRA and thus can be used in some cases. SP is also the primary drug of choice for initially treating ascites due to cirrhosis and can be used in doses up to 400 mg per day to achieve optimal sodium excretion [12]. Lastly, both SP and eplerenone have been used in the treatment of diabetic kidney disease [13], where these MRAs can protect against organ damage. Thus, there are multiple related conditions in which SP may have therapeutic benefit.

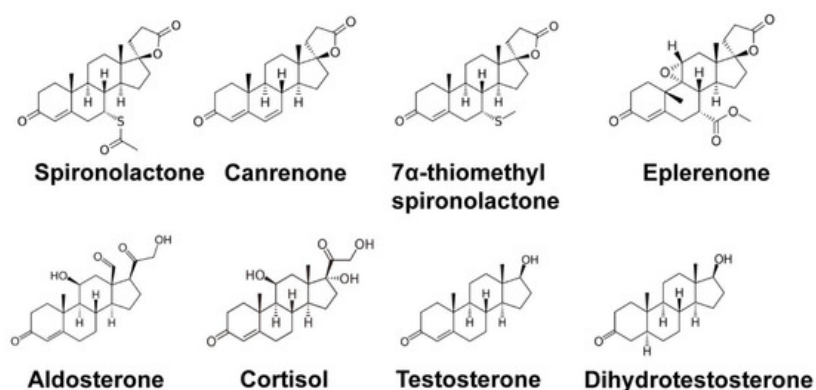


Figure 2. Structures of spironolactone and related molecules. Chemical structures are provided for spironolactone, its metabolites canrenone and 7α-thiomethylspironolactone, the mineralocorticoid receptor antagonist eplerenone, the mineralocorticoid agonist aldosterone, the related molecule cortisol, and the androgen receptor agonists testosterone and dihydrotestosterone.

2.2. SP as an Androgen Receptor Antagonist

Though SP has been successfully used for hypertension and heart failure, the feminizing effects of the drug in males, such as gynecomastia, were also noted [14]. During the 1970s, SP was found to antagonize androgen receptors (ARs) [15][16], which explains the unique effects of SP in males. However, AR antagonism ultimately led to the use of SP in a variety of for androgen-associated skin conditions (Figure 2), including acne and hair growth dysfunction [17][18]. Acne is best understood as a disease of excessive sebum production which consequently leads to blocked pilosebaceous follicles by way of undifferentiated keratinocytes, resulting in a lipid-rich environment for *Propionibacterium acnes* to thrive [19]. An adaptive and innate immune reaction is triggered, resulting in the recruitment of leukocytes to the blocked pilosebaceous follicles and causing the erythematous reaction seen in acne. Dihydrotestosterone (DHT) binds to the androgenic receptors within the pilosebaceous follicles prompting the release of sebum, a lipid-rich material that coats the hair follicles. Increased sebum levels of androgens seen in adolescent males and females undergoing puberty results in acne vulgaris commonly seen within this population. Thus, the result of blocking these androgens from binding to ARs within the sebocytes by SP would lead to less sebum production and a reduction in inflamed pilosebaceous glands.

A plethora of studies have demonstrated the safety and tolerability of spironolactone at low doses for acne treatment in women [17][18][20]. These doses typically range from 25 to 200 mg per day in one to two divided doses. However, spironolactone has seen a dramatic increase in dosage among two particular demographics: patients with female pattern hair loss (FPHL) and transgender women. SP has been shown to arrest hair loss progression and stimulate partial hair regrowth. The typical dose for non-transgender women being treated for either acne or hair loss is typically 200 mg; however, doses as high as 400 mg/day have been reported without any profound effects [21]. The two most commonly

used anti-androgen therapies for feminizing hormone therapy are cyproterone acetate (CPA) and spironolactone. However, despite both hormone therapies having a similar mechanism of action, which involves inhibiting the binding of androgens to androgen receptors and reducing androgen biosynthesis, studies have shown a possible link between CPA and liver toxicity [22]. For this reason, CPA is not currently approved in the United States, making spironolactone the more popular of the two worldwide. Current practice guidelines have established 400 mg/day as the safety cut-off for male-to-women spironolactone regimens [23].

In addition to antagonizing the androgen receptor, SP has also been reported to interfere with a cofactor of cytochrome P450 necessary for testosterone synthesis, increase the level of sex hormone binding globulin, and reduce 5 α -reductase activity [24][25]. Thus, there may be other mechanisms by which SP may impact androgen signaling in vivo.

3. The XPB Protein as a Novel Target of Spironolactone

3.1. Identification of the DNA Repair Protein XPB as a Target of SP

The disparate studies highlighted above may suggest that SP has many new targets in cells besides the MR and AR. However, the study by Alekseev et al. provided the first indication that a single protein may explain the diverse effects of the drug. As described above, the authors noted that SP inhibited the removal of UV photoproducts from genomic DNA [3]. This process solely occurs via the NER machinery in human cells and requires nearly 20 polypeptides spread among 6 different core factors [26]. By examining the protein levels of these NER factors, Alekseev et al. observed that only one protein, XPB (xeroderma pigmentosum group B), was rapidly and specifically lost upon SP treatment [3].

XPB is mutated in humans with the disease xeroderma pigmentosum, who are photosensitive and generally exhibit higher rates of skin cancer [27][28]. XPB exists as a component of a larger protein complex known as TFIIH (transcription factor II-H) [29][30][31] (Figure 3A). TFIIH is essential for the removal of UV photoproducts and other bulky adducts from DNA by the NER machinery. In NER, DNA lesions are removed from DNA in the form of small DNA oligonucleotides approximately 30 nt in length via a dual incision mechanism [26] (Figure 3B) that remain bound to TFIIH following their excision [32][33]. For the XPF and XPG endonucleases to incise at sites bracketing the lesion, the DNA must be unwound around the lesion. Though the XPD subunit of TFIIH possesses the primary helicase activity responsible for unwinding DNA around the lesion, the ATPase activity of XPB is thought to help to anchor TFIIH to the chromatin [34] and to separate the two strands of DNA around the lesion so that XPD can bind, further unwind DNA, and verify that a lesion is present [29][35]. Thus, in the absence of XPB function due to genetic mutations or SP treatment, the DNA lesions are unable to be properly processed and excised from the genome. This lack of lesion removal therefore provides an explanation as why NER is inhibited by SP and why SP was found to sensitize cells to UV radiation and cisplatin [3][36][37][38]. Given the wide variety of DNA damaging agents that induce lesions targeted for removal by NER, SP could be used to improve the effectiveness of DNA damaging anti-cancer drugs in many different cancer types. Indeed, a preclinical study showed that sensitivity of treatment of multiple myeloma cells to the alkylating agent melphalan could be improved by co-treatment with SP [39]. However, many chemotherapies induce side effects that could be worsened by treatment with SP. For example, a recent study monitoring cisplatin-induced peripheral neuropathy in mice demonstrated that SP worsened this condition [40].

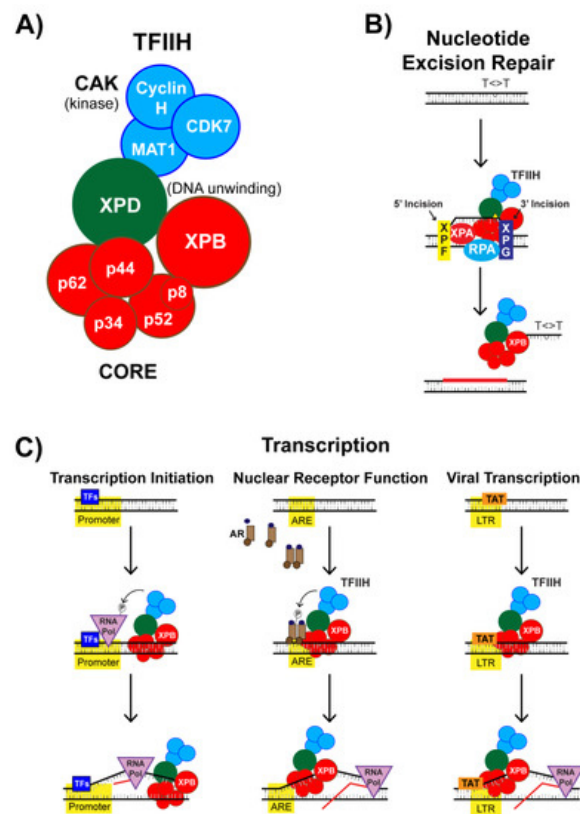


Figure 3. TFIID structure and function. **(A)** TFIID (transcription factor II-H) is a 10-subunit protein complex with multiple enzymatic activities, including kinase activity from its cyclin-dependent kinase-activating kinase sub-complex and DNA unwinding activity from the XPD and XPB subunits. **(B)** TFIID functions in nucleotide excision repair (NER) to unwinding DNA so that the XPA and XPG endonuclease can incise the damage strand of DNA 3' and 5' to the lesion, respectively, which releases the damage-containing DNA oligonucleotide in complex with TFIID. **(C)** TFIID also functions in general transcription initiation (**left**), nuclear receptor-dependent transcription (**middle**), and in viral transcription (**right**).

XPB has not been reported to be involved in DNA double-strand break (DSB) repair, and thus the discovery that SP inhibited homology-directed DSB repair [4] may be somewhat more difficult to reconcile. However, mutations in the XPD component of TFIID have been reported to interfere with transcription-associated recombination in mammalian cells [41] and to cause replication fork breakage and restart in budding yeast [42]. Moreover, mass spectrometric analyses of proteins enriched at replication forks stalled by hydroxyurea treatment revealed the presence of several components of TFIID, including XPB [43]. Furthermore, a recent study found that SP sensitized cancer cells to the nucleoside analog gemcitabine and the PARP inhibitor osimertinib both in vitro and in mice in vivo [44]. Both compounds do not induce DNA damage directly and can instead interfere with replication fork progression and stability that could collapse to generate DSBs. Thus, it is possible that XPB-containing TFIID complexes function in some capacity at stalled replication forks, double-strand break repair intermediates, or at collisions between the replication and transcription machineries, all of which may generate DNA structures that require the DNA unwinding functions of TFIID. However, further studies are clearly needed to better understand how SP inhibits other genome maintenance pathways besides NER.

3.2. SP Impacts TFIID Function in Transcription Initiation

As its name implies, TFIID also functions to promote the initiation of gene transcription via two key enzymatic functions [29] [30]. The first and potentially most important function involves the XPB subunit of TFIID, which promotes the opening of DNA at gene promoters via ATP-dependent DNA translocase activity [45][46]. This DNA strand separation is necessary for transcription initiation so that a single-stranded template DNA can engage the active site of RNA polymerase II for transcription initiation (Figure 3C, left), and thus, XPB is thought to act as a molecular wrench in this context to open promoter DNA. A second activity of TFIID is found with the cyclin-dependent kinase (CDK)-activating kinase (CAK) subcomplex (Figure 3A), which is composed of CDK7, Cyclin H, and MAT1. CDK7 promotes transcription via the phosphorylation of several proteins, including RNA Polymerase II, the positive transcription elongation factor b (p-TEFb), and various transcription factors.

Consistent with the general transcription function of XPB and TFIID, other experimental evidence indicates that SP can inhibit gene expression in vitro and in vivo. For example, though antagonism of the MR receptor by SP is the classical model for how SP improves endothelial dysfunction and survival in heart failure, recent work suggests that SP may prevent inflammation in target tissues by interfering with the expression of pro-inflammatory gene products [47]. For

example, Elinoff et al. showed that SP, but not the MR antagonist eplerenone, suppressed NF- κ B and AP-1 reporter activity in cells in vitro independent of the MR, AR, or glucocorticoid receptor (AR), and this phenotype could be counteracted by overexpression of XPB [47]. SP treatment was further shown to be associated with low levels of RNA polymerase II and XPB at the IL-8 promoter in TNF α -treated pulmonary artery endothelial cells in vitro. Lastly, additional studies demonstrated that SP decreased XPB protein levels in whole lungs of a rat model of pulmonary hypertension and reduced the levels of several inflammatory cytokines in the serum of pulmonary arterial hypertension patients. Thus, via inhibition of TFIIH function in transcription initiation, SP may interfere with the transcriptional induction of pro-inflammatory genes in hypertension.

3.3. Nuclear Receptor-Dependent Transcription is Regulated by TFIIH and SP

Upon binding to their cognate ligand, nuclear receptors (NRs) facilitate the transcription of specific gene networks [48]. NRs directly associate with transcription factors, including with TFIIH, to mediate gene transactivation (Figure 3C, middle). NRs can also be targeted for phosphorylation by CDK7 within TFIIH to promote the recruitment of other transcriptional co-activators to enhance transcription or to terminate the ligand response [49]. For example, TFIIH promotes both AR-dependent transactivation at promoters and AR turnover [49]. These results suggest that some of the anti-androgen activity of SP may not only be due to direct antagonism of the receptor but also to altered transcription initiation at AR-regulated genes.

In addition to inhibiting transcription, other NR promoter activities may be stimulated by SP. For example, the work described above showing that SP induced an up-regulation of NKG2DL expression in colorectal cancer cells identified the nuclear hormone receptor (RXR γ) as responsible for this upregulation [2]. Reporter assays confirmed that SP treatment increased RXR γ promoter activity. However, the precise mechanism by which affects NKG2DL expression may be complex, as loss of RXR α instead increased NKG2DL expression. Thus, the regulation of NKG2DLs by RXR family members and the impact that SP has on modulating transcriptional responses remained to be better defined. Nonetheless, the genomic stress response kinases ATM and ATR had previously been reported to be required for NKG2DL expression [50], and Leung et al. observed that ATM-CHK2 pathway was specifically activated in an RXR γ -dependent manner in colorectal cancer cells [2]. Thus, though questions remain regarding how SP induces NKG2DL upregulation, the involvement of the NR RXR γ is consistent with the hypothesis that SP may be working through the function of XPB/TFIIH on NR function in gene transactivation.

3.4. SP Impacts TFIIH Function in Viral Transcription

It is well-recognized that many viruses co-opt the human host cell replication and transcription machinery to enable the production of more virions. For example, the HIV-1 transcription activator Tat protein is necessary for transcription of viral genes [51][52]. In addition to binding to the transactivation response element (TAR) in the nascent viral RNA [53], Tat is also known to interact with several basal transcription factors at the HIV-1 promoter to stimulate transcription [54], including by binding directly to the CAK complex of TFIIH [55][56]. Tat also interacts with p-TEFb to promote transcription elongation by enhancing p-TEFb recruitment and release of paused RNA polymerase II at the HIV-1 promoter (Figure 3C, right).

Interestingly, XPB has previously been reported to impact HIV-1 infection. Though early studies indicated XPB may protect against retroviral infection [57][58], other screening work suggested that XPB was required for HIV-1 production [59][60]. Based on the finding that SP caused the rapid degradation of XPB [3], Lacombe et al. used SP treatment to determine whether SP could affect HIV-1 transduction in vitro [61]. The authors found that SP, but not eplerenone, caused a loss of XPB protein expression in T cells in vitro and inhibited HIV-1 and HIV-1 transduction. Consistent with the known role of XPB in transcription, SP was also observed to inhibit Tat-dependent promoter activity. A recent study further suggested a similar effect for SP in T-cells infected with human T-cell lymphotropic virus type 1 (HTLV-1) [62], in which the HTLV-1 Tax oncoprotein interacts with XPB to promote TFIIH-dependent transcription at the viral promoter. Along with the previous screening study that identified SP as an inhibitor of EBV SM protein-dependent transcription and virus production [5], these results imply a common mechanism for SP function as an anti-viral compound: SP-induced loss of the XPB protein likely interferes with the ability of viral proteins to co-opt TFIIH and the host cell transcription machinery to transcribe viral genes.

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