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Targeting androgen-independent pathways: new chances for patients with prostate cancer?

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ABSTRACT

Androgen deprivation therapy (ADT) is the mainstay treatment for advanced prostate cancer (PC). Most patients eventually progress to a condition known as castration-resistant prostate cancer (CRPC), characterized by lack of response to ADT. Although new androgen receptor signaling (ARS) inhibitors and chemotherapeutic agents have been introduced to overcome resistance to ADT, many patients progress because of primary or acquired resistance to these agents. This comprehensive review aims at exploring the mechanisms of resistance and progression of PC, with specific focus on alterations which lead to the activation of androgen receptor (AR)-independent pathways of survival. Our work integrates available clinical and preclinical data on agents which target these pathways, assessing their potential clinical implication in specific settings of patients. Given the rising interest of the scientific community in cancer immunotherapy strategies, further attention is dedicated to the role of immune evasion in PC.

1. Introduction

Prostate cancer (PC) accounts for 1 in 5 new diagnoses of cancer in the United States of America and, despite the recent improvements, this neoplasm still causes more than 26,000 deaths per year (Siegel et al., 2016). The prostate gland is constituted both of basal and luminal epithelium arranged in a fibro-muscular stromal network (Packer and Maitland, 2016). Based on the observation that human PC are mostly luminal-like adenocarcinomas, the luminal origin of PC is supported by several studies (Wang et al., 2009; Wang et al., 2014). However, the basal cell transformation into tumorigenic luminal cells is also suggested as an alternative origin of PC (Packer and Maitland, 2016). Differently from basal cells, the luminal secretory cells of normal prostate require androgens for survival and undergo apoptosis upon androgen withdrawal (Long et al., 2005). Therefore, the androgen receptor (AR) has been historically considered the most relevant target to control the growth and dissemination of PC and this notion has guided the treatment of PC for several years (Watson et al., 2015). The time has probably come for this paradigm to be changed. First, not all hormone-naïve PC appear to be equally responsive to androgen deprivation therapy (ADT). Recently, Feng et al. segregated more than 3500 PC samples into luminal A, luminal B, and basal subtypes using the PAM50 classifier, which distinguishes basal and luminal breast cancers, and showed that only luminal B PC are significantly associated with post-operative response to ADT (Feng et al., 2017). Second, the high frequency of AR aberrations, found in highly pretreated patients with PC, suggests that AR probably acts as the main driver of proliferation and progression in some of these patients too, but this observation does not tell the whole story (Robinson et al., 2015). In fact, the poorly differentiated and aggressive PC cells show low levels of AR and prostate specific antigen (PSA) expression and sustain proliferation and invasion in a completely hormone-independent manner (Ellis and Loda, 2015; Miyamoto et al., 2015). Stemness signatures, self-renew capacity, resistance to immune-response, phenotypic plasticity and lack of contact inhibition are the main characteristics of these clones, which are refractory to therapies, exhibit high clonogenic potential, and show long-term tumor-propagating capacity (Boyd et al., 2012; Ellis and Loda, 2015; Mahal et al., 2016; Qin et al., 2012; Roubaud et al., 2016). These cells may be the result of multiple genetic and phenotypic alterations induced by treatments, but may also represent pre-existing

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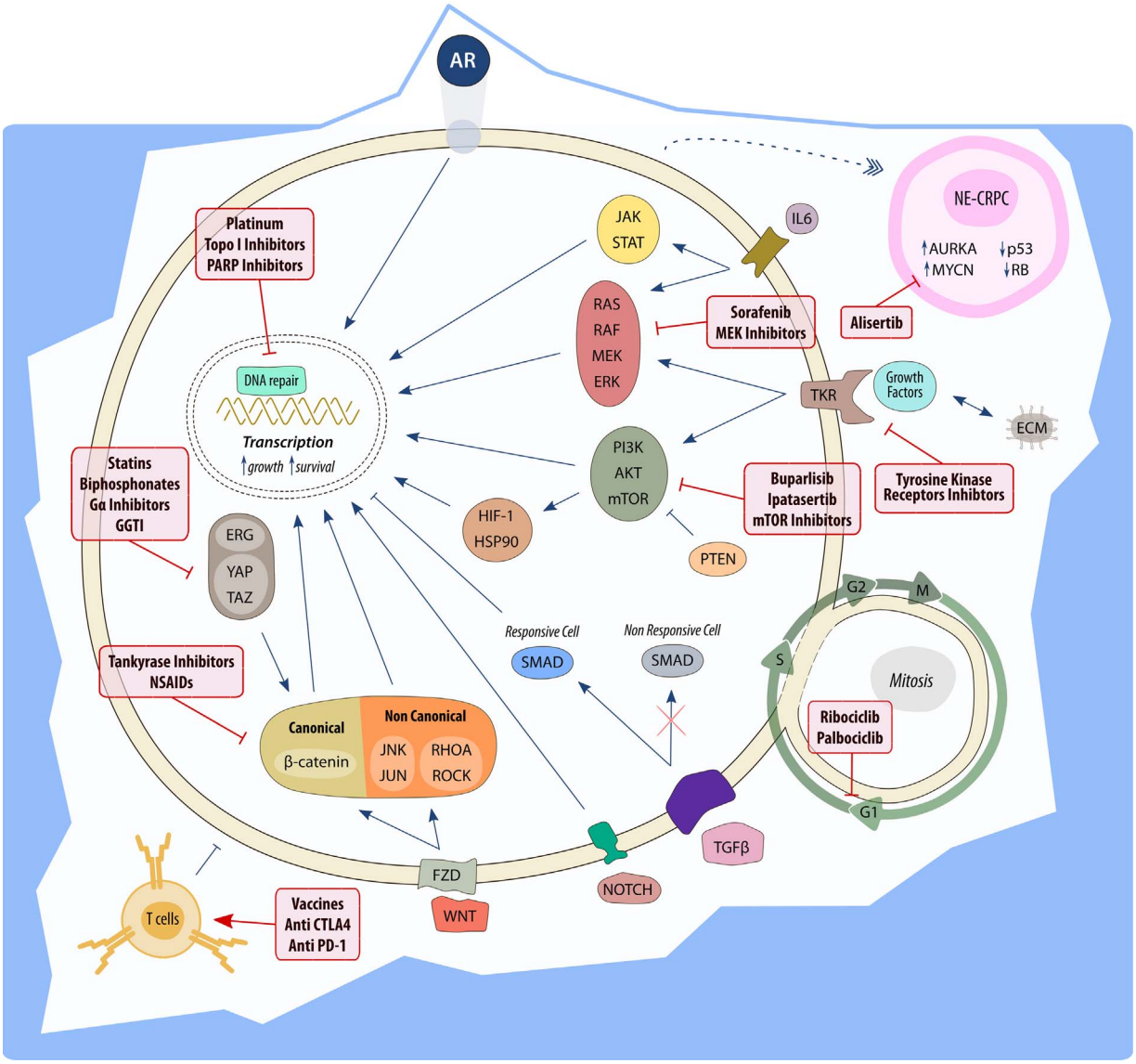

Fig. 1. The iceberg of resistance in PC. The AR alterations (i.e. mutations, amplifications, truncations) only represent the tip of the iceberg. Below we report a selection of AR-independent pathways potentially involved in the resistance of PC cells to treatments. Several drugs are currently available for inhibiting these pathways. Clockwise: (A) Divergent clonal evolution from CRPC adenocarcinoma cells is implicated in the development of NEPC; alisertib is effective in tumors which harbor amplifications of MYCN and AURKA. (B) IL-6 promotes PC cell proliferation and induces EMT through multiple signal pathways, including the JAK-STAT and the ERK-MAPK pathway. (C) Several components of the ECM influence the tumor microenvironment and activate the RAF-MEK-ERK kinase cascade and the PI3K-AKT-mTOR pathway. The hypoxia pathway is intimately connected with the PI3K-AKT-mTOR pathway. As shown, sorafenib, MEK inhibitors, buparlisib, ipatasertib and mTOR inhibitors are all potential modulators of these signaling pathways. (D) Palbociclib and ribociclib inhibit CDKs, inducing the blockade of cell cycle progression. (E) TGFβ exerts pleiotropic actions on immune cells and promote angiogenesis in PC; a models suggests that tumor cells may become resistant to TGFβ trough inactivation of TGFβ receptor or SMAD activity (Pickup et al., 2013). (F) Notch shows both tumor suppressive and oncogenic roles in PC, inducing the activation of several transcription factors. (G) Canonical (β-catenin-dependent) and non-canonical (RHOA, ROCK and JNK dependent) Wnt signaling exerts proliferative effects on tumor cells. ERG activates YAP transcriptional program and YAP/TAZ pathway acts on Wnt signaling. Tankyrase inhibitors, statins, NSAIDS, bisphosphonates, Gα inhibitors and GGTI potentially modulate these pathways. (H) Immunotherapy strategies block the inhibitors signals occurring on T-cells, thus reversing the inactivation of immune response against tumor cells. (I) PARP inhibitors block the repair of SSBs, induced by endogenous damages; cells with functional HR are able to repair more genotoxic DSBs produced by cytotoxic agents, but not BRCA 1 and 2 mutant cells, which undergo cell death. *AKT: protein kinase B; Anti-CTLA-4: anti-cytotoxic T-lymphocyte antigen 4; Anti-PD-1: anti-programmed cell death protein 1; AR: androgen receptor; AURKA: aurora kinase A; CRPC: castration-resistant prostate cancer; ECM: extracellular matrix; ERG: erythroblast transformation-specific related gene-1; ERK: extracellular signal-regulated kinase; GGTI: inhibitors of geranylgeranyl transferase-1; HIF1α: hypoxia-inducible factor 1-alpha; HSP90: heat shock protein 90; IL-6: interleukin-6; Fzd: frizzled; JAK: janus kinase; JNK: c-Jun N-terminal kinases; MAPK: mitogen-activated protein kinase; MEK: mitogen-activated protein kinase kinase; mTOR: mammalian target of rapamycin; MYCN: v-myc avian myelocytomatosis viral oncogene neuroblastoma derived; NEPC: neuroendocrine prostate cancer; NSAIDS: nonsteroidal anti-inflammatory drugs; p53: tumor protein p53; PARP: poly ADP-ribose polymerase; PC: prostate cancer; PI3K: phosphoinositide 3-kinase; PTEN: phosphatase and tensin homolog; Raf: rapidly accelerated fibrosarcoma; Ras: rat sarcoma; RB: retinoblastoma product; RHOA: ras homolog gene family, member A; ROCK: rho-associated protein kinase; SMAD: small mother against decapentaplegic; STAT: signal transducer and activator of transcription; TAZ: transcriptional coactivator with PDZ-binding motif; TKR: tyrosin kinase receptor; TGFβ: transforming growth factor-beta; VEGF: vascular endothelial growth factor; YAP: Yes-associated protein; Wnt: wingless-related integration site.*

subpopulations, which are selected based on their ability to survive in adverse conditions. Genomic rearrangements, rare mutations and epigenetic phenomena amplify transcriptomic diversity of PC, converging on specific cellular functions and AR-independent signaling pathways of survival and proliferation (Wyatt et al., 2013) (Fig. 1). Therefore, primary or acquired resistance to treatments is probably the result of the extensive genetic diversity and heterogeneity of PC rather than of a linear evolutionary process (Boyd et al., 2012; Liu et al., 2015). In addition to genetic or epigenetic events that occur in tumor cells, a favorable local microenvironment is an invariable prerequisite for the growth and the dissemination of this neoplasm (Barron and Rowley, 2012). Chemo-hormonal and mechanical signals modulate the behavior