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New insights into prostate cancer progression: A focus on vitamin D signaling

Vanessa Friedrich, Gilles Laverny *

Institut de Génétique et de Biologie Moléculaire et Cellulaire, Université de Strasbourg, CNRS, Inserm, UMR 7104- UMR-S 1258, Illkirch, France

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ABSTRACT

Prostate cancer (PCa) is one of the most frequent cancer in men of western society. Whereas the therapeutic options for localized PCa are efficient, those for advanced forms lead to resistance and are of a poor outcome. Thus, it is of utmost importance to understand the mechanisms underlying PCa progression to identify biomarkers predicting tumor evolution and novel therapeutic options. This review summarizes the current knowledge on PCa progression, treatments and preclinical approaches, with a specific emphasis on the role of vitamin D signaling.

1. Epidemiology, progression, and treatments

Prostate cancer (PCa) is the most commonly diagnosed cancer and the second leading cause of cancer-related death in men of the western society [1]. Since 2014, PCa incidence is globally rising by 3% per year and is predicted to increase from 1.4 to 2.9 million new cases worldwide over the next two decades [2], resulting in a major burden to the healthcare system. PCa is a slow-growing tumor with an evolution spanning for decades. Prostatic intraepithelial neoplasia (PIN) resulting from the hyperproliferation of prostatic epithelial cells (PECs) is considered as the precursor for prostatic adenocarcinoma (AdC) in 95% of the cases [3]. The remaining 5% are rare subtypes such as neuroendocrine, sarcomatoid, adenosquamous or signet ring cell with more aggressive features [4,5]. The evolution from PIN towards AdC spans several years to decades, with an eventual spreading into distant organs such as bones in 84%, lymph nodes in 10.6% and liver in 10.2% of the cases [6]. The relatively advanced median age at diagnosis (65–69 years old) is mainly due to the prolonged and gradual nature of this transition [7]. Diagnosis is mainly based on blood testing of Prostate Specific Antigen (PSA) levels, and when above 20 ng/mL, associated with histological imaging. However, because PCa screening methods lack reliability, especially for aggressive forms, there is a high number of patients that are newly diagnosed with metastatic disease, also referred to as metastatic hormone sensitive PCa (mHSPC) (currently 5–10% of patients representing 50% of the PCa-related deaths) [7–9].

PCa severity is histologically distinguished and classified through the use of the Tumor Node Metastasis (TNM) nomenclature, as well as the International Society of Urological Pathology (ISUP) and Gleason scores (Fig. 1, Tables 1 and 2) [10–12]. The TNM score characterizes PCa invasiveness. T, for tumor, represents the extent of PCa within the prostate, whereas N and M relate the invasion into lymph nodes and/or distant organs. ISUP and Gleason scores enable a stratification of the tumor aggressivity through histological features (Fig. 1). According to the 2019 ISUP Consensus Conference [13], there are two main histological features characterizing PCa: Intraductal carcinoma (IDC) and invasive carcinoma. IDC is defined by a proliferation of cancer cells within the preexisting ducts with a preservation of basal cell integrity surrounding the duct. In contrast, invasive carcinoma is characterized by the loss of the basal cell layer and cancer cell proliferation into the stroma. In 2024, the ISUP Consensus working group 1 suggested IDC to be one of the putative precursors of invasive PCa [14]. IDC is believed to be accompanied by invasive carcinoma in 99% of prostate biopsies. However, if IDC is detected alone, no ISUP or Gleason grading should be assigned, and no radical therapy applied. IDC can exhibit either solid, papillary or cribriform architecture (Fig. 2). Cribriform IDC has been associated with a worse prognosis compared to poorly formed invasive carcinoma.

At diagnosis, 75% of patients present localized PCa associated with a 5-year overall survival of nearly 100% [7]. At this stage, with a low PCa grade (ISUP1 - T1/2N0M0), an active surveillance is systematically offered to defer and reserve radical treatments only for patients whose disease is progressing during follow-up. Low dose rate brachytherapy is

* Corresponding author.
E-mail address: laverny@igbmc.fr (G. Laverny).

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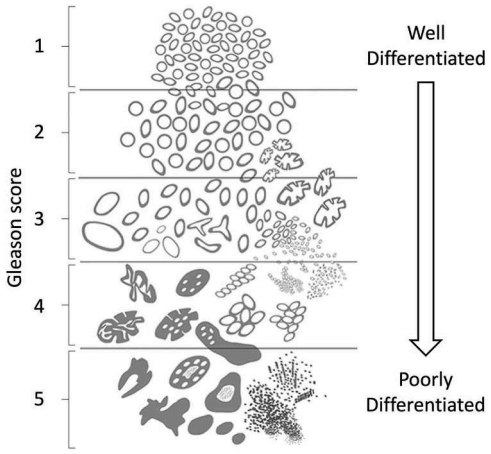

Fig. 1. Gleason grading system. Gleason score is based on histological grading and depicts the sum of the two most severe lesion type. This score can be converted to ISUP grade (see Table 1). Adapted from [6].

Table 1
Risk classification through Gleason, ISUP and/or PSA levels.

Gleason score (sum of the two most severe lesion type)	**ISUP score**	**Aspects of the glands**	**PSA level (ng/mL)**	**Risk category**
2–6	1	Well-differentiated	< 10	Low / No cancer
3 + 4 (majority of 3) = 7	2	Moderately differentiated	10–20	Favorable Intermediate
4 + 3 (majority of 4) = 7	3	Moderately differentiated	10–20	Unfavorable Intermediate
4 + 4 = 8 3 + 5 = 8 5 + 3 = 8	4	Poorly differentiated	> 20	High
9–10	5	Not differentiated	> 20	Very high

Table 2
TNM classification of prostatic tumors.

Tumor		**Lymph Nodes**		**Metastasis**	
1	Non-visible	0	No dissemination	0	No dissemination
2	Confined in the prostate	1	Dissemination	1	Dissemination
3	Exceed the prostate				
4	Extend to neighboring organs				

an alternative option, when patients refuse the active surveillance. However, when the PCa is diagnosed with ISUP ≥ 2 or TxN0M0, the treatments of choice are radical prostatectomy and/or external beam radiation therapy (Fig. 3). For PCa locally or metastatically resuming disease, and/or being initially diagnosed with grade being above ISUP4 with an eventual spreading into nearby lymph nodes or distant organs, hormonal therapy is the first line of treatment to control tumor growth (Fig. 3). As androgens (e.g. testosterone and dihydrotestosterone) promote PCa growth through activation of the androgen receptor pathway, hormonal therapy aims to deprive the tumor of androgen stimulation, either through surgical (e.g. orchiectomy) or pharmacological castration. The latter is based on the administration of Androgen Deprivation Therapy (ADT) (e.g. leuprolide, degarelix, relugolix) and/or Androgen Receptor Pathway inhibitors (ARPi) (e.g. abiraterone, enzalutamide, apalutamide and darolutamide). Anti-androgen therapies present substantial adverse effects, such as osteoporosis, increased blood sugar and cholesterol levels, as well as psychological issues [15].

ADT constitutes the backbone of systemic therapy for advanced PCa. Although, most patients are early responders to the initial hormonal therapy, they often relapse and ultimately progress to castration-resistant PCa (CRPC). This aggressive state is associated with metastatic dissemination in most patients and significantly reduces the 5-year survival rate [7]. The standard of care for metastatic PCa, with or without castration resistance, is based on combining ARPi with ADT [16–19]. As the tumor progresses, ARPi or ADT alone [20,21] or combined [22–24] are associated to taxane-based chemotherapy (e.g. docetaxel or cabazitaxel) (Fig. 3). However, the benefits of chemotherapy supplementation is limited as it extended the overall survival of advanced metastatic PCa to approximately one year as reported by the STAMPEDE (2016) [20] and CHAARTED (2015) [21] clinical trials. Moreover, the overall survival extension is limited to 4 months for metastatic CRPC (mCRPC). The 14-year follow-up of the STAMPEDE clinical trial associated to the CHAARTED trial [25] indicates a higher response to chemotherapy in PTEN inactivated metastatic PCa when the decipher score is above 0.8. The decipher score depicted the expression of 22 genes identified by the company Veracyte to be biomarkers of cancer aggressivity which enable the classification of patients regarding their risk category [26]. Recently the decipher score has been correlated to unfavorable histological features including IDC and Cribriform IDC [27]. However, the increase in 5-year mean survival time in this sensitive population is limited to 9 months.

Recently, the combination of ADT and ARPi has been extended to high-risk metastatic and non-metastatic PCa to control systemic cancer cell dissemination. Thus, in metastatic disease, it slows down cell dissemination [19,23,28], and in non-metastatic castration-resistant prostate cancer or high-risk biochemical recurrence, it prolongs metastasis-free survival [29–31]. Note that high-risk biochemical recurrence is defined by PSA relapse after definitive local therapy with a high likelihood of subsequent metastatic progression.

The tumor microenvironment (TME) of PCa is very complex, including various cell types such as immune, stromal, and endothelial cells that communicate with cancer cells to either promote or slow down tumor progression. Even though PCa is considered to be a cold tumor, defined by an immunosuppressive TME resulting in sparse effector T-lymphocytes infiltration, immunomodulators are currently being considered as potential approaches for the treatment of advanced PCa and mCRPC. The most common being Sipuleucel-T using a fusion protein coupled to patient's peripheral blood mononuclear cells (PBMC), and immune checkpoint inhibitors targeting PD-1/PDL-1 enhancing immune cells activity of the TME by boosting the patient's effector T-lymphocytes to promote tumoral cell elimination [32,33]. Additional strategies include PARP inhibitors targeting the DNA repair mechanism in tumor cells, or Radium-223 dichloride, an alpha-emitting radiopharmaceutical targeting bone metastasis. However, clinical trials failed to show significant improvement [32–35]. T-cell engager bispecific antibodies targeting key antigens (e.g. PSMA, STEAP1, KLK2) or novel PSCA-CAR T cell therapies are currently being tested in Phase I/II as a therapeutic option for mCRPC [36–39].

Given the current low efficiency of advanced PCa treatments, a better understanding of the mechanisms driving the progression of advanced and metastatic PCa is essential for identifying new biomarkers that can guide the development of more effective therapies and improve diagnostic precision based on disease aggressiveness.

2. PCa preclinical models

Being a slow-growing tumor that evolves over decades, collecting repeated biopsies over time to study tumor evolution in men is unethical. Therefore, it is of utmost importance to establish relevant disease models to gain accurate understanding of tumor pathogenesis and to shed light on efficient biomarker and treatment strategies. Plenty of PCa preclinical models were developed with various complexity and physiological relevance, giving each of these models' advantages and

limitations regarding the research topic. Cell culture in 2D and 3D using immortalized PCa cell lines (e.g. LNCaP, VCap, PC-3, DU145, MDA-PCa, or IGR-Cap1), because of its ease and reproducibility, are widely used and enabled a great advancement for understanding PCa tumor biology [40–42]. The characteristics of available PCa cell lines have recently been summarized [41]. However, these cell lines face serious limitations [43]. To begin with, most of the available human PCa cell lines cited above are derived from metastasis in the bone (e.g. VCap, PC-3, MDA-PCa), lymph node (e.g. LNCap), brain (e.g. DU-145), or from primary rare basal and stem-like PCa (e.g. IGR-Cap1) [44], and thus do not reflect the heterogeneity of the initial tumor. This can be explained by the fact that primary tumor cells fail to adapt to long-term culture *in vitro* [45], in line with a recent study using patient-derived organoids (PDO) [46]. Cultured cells represent a valuable tool for the initial step of drug effect screening, as well as for elucidating basic molecular mechanisms involved in cancer cell progression. However, relying predominantly on immortalized cells is limiting, as it fails to capture cancer heterogeneity and complex interplay with the microenvironment underlying disease progression.

Coculture systems, or microfluidic tools, in 2D or 3D, partially mimic physiological interactions or behaviors. However, the interactions remain limited to a few cell types simultaneously, failing to reproduce the complex interaction between tumoral cells and the microenvironment.

3. Patient-derived organoïds (PDOs) as a model for personalized medicine approaches

Given the substantial heterogeneity across PCa patients, as well as the multifocal nature of the disease and the intrinsic molecular diversity found within individual lesions, models that faithfully retain patient-specific features are essential for advancing precision medicine. Recent progress enabled to improve PDO culture. Novel extracellular matrix (ECM)-free culture conditions using ultra-low attachment plates manage to improve PDO growth and to maintain cellular heterogeneity from patients' biopsies [46,47]. Thus, PDOs enable the reproduction of intrinsic drug response patterns, making them a well-suited tool for personalized medicine strategies. However, despite capturing key aspects of cancer complexity, PDOs remain limited to few passages with uncertain success rates given the patient biopsies' heterogeneity in terms of quality, proliferation capacity and available biological material. While short-term PDO cultures are not compatible with long-term investigation of PCa pathogenesis, they are highly suitable for orienting clinical treatment decisions. Current stratification strategies rely on transcriptomic profiling associated or not to histopathological spatial approaches and machine-learning algorithms that integrate multi-omic and imaging data to predict disease behavior and treatment response [47,48]. As an example, this translates into the identification of a predictive tyrosine kinase inhibitor response for the treatment of PCa. Patients can be then stratified regarding their transcriptomic signature (e.g. androgen, hypoxia or p53 pathway activity) for the administration of the most efficient tyrosine kinase inhibitors. [47].

In addition, microfluidic tools, and especially the emerging projects to generate a "prostate-on-chip" [49] or even a "body-on-a-chip" [50], are very promising for improving physiological relevance and the modelling of interaction between different cell types and organs. However, given the complexity of maintaining PDO in culture, incorporating features such as long-term 3D culture with stromal and endothelial compartments, or the addition of circulating immune cells require substantial optimization, and standardized protocols are still lacking. Moreover, commonly used materials such as polydimethylsiloxane (PDMS) are known to absorb hydrophobic drugs and steroid hormones, which is particularly problematic given the omnipresence of hydrophobic drugs in the treatment of PCa. Thus, for drug screening applications, alternative low-adsorption polymers compatible with quantitative microscopy and regulatory standards are required [51], increasing fabrication cost and technical complexity.

Recently, an alternative approach for maintaining PDO over time without disrupting patient specific heterogeneity or drug response has been reported. The concept relies on xenografts series, which have been validated using tumors from a patient with mHSPC or mCRPC [52]. Although serial transplantation should be extended to a larger cohort of patients across different disease stages, these findings open new opportunities for maintaining PCa patient tissue either in a static or dynamic system, enabling the identification of valuable patient-specific molecular signatures for translational research.

Thus, both PDOs and microfluidic systems aim to provide a window for treatment stratification and personalized medicine. Even though these technologies are encouraging, they remain in their early stages of development.

4. Pivotal mouse model development for the investigation of PCa pathogenesis

As described above, a widely used strategy to maintain cancer cell lines or heterogeneous patient tumors within a complex TME is based on

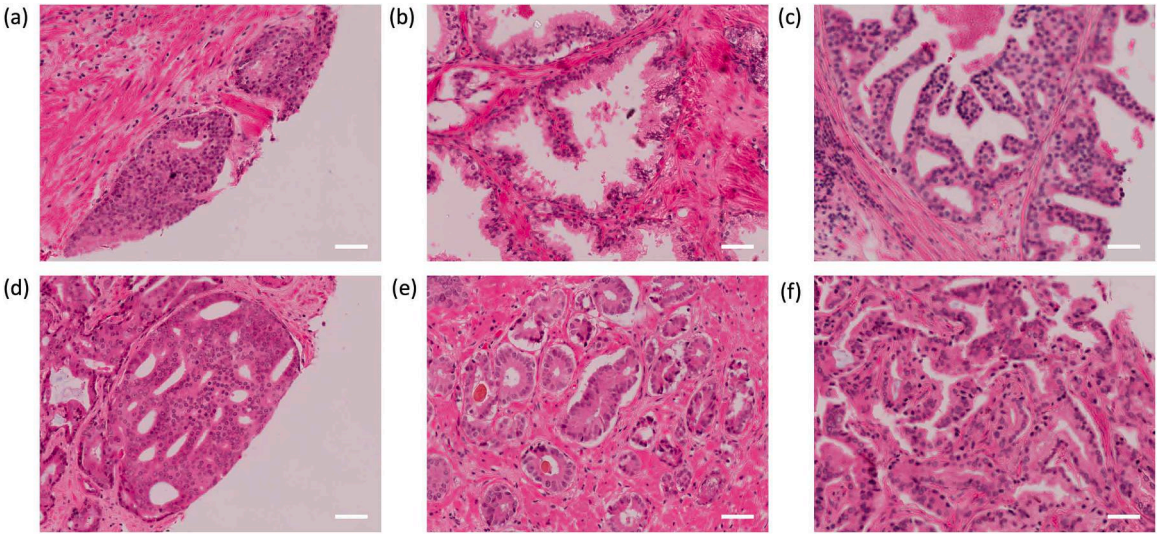

Fig. 2. Histological representation of human IDC and invasive tumors. (a) Solid IDC. (b) loose papillary IDC. (c) dense papillary IDC. (d) Cribriform IDC. (e) ISUP2 invasive tumor. (f) ISUP3 invasive tumor. Scale bar = 50 μm.

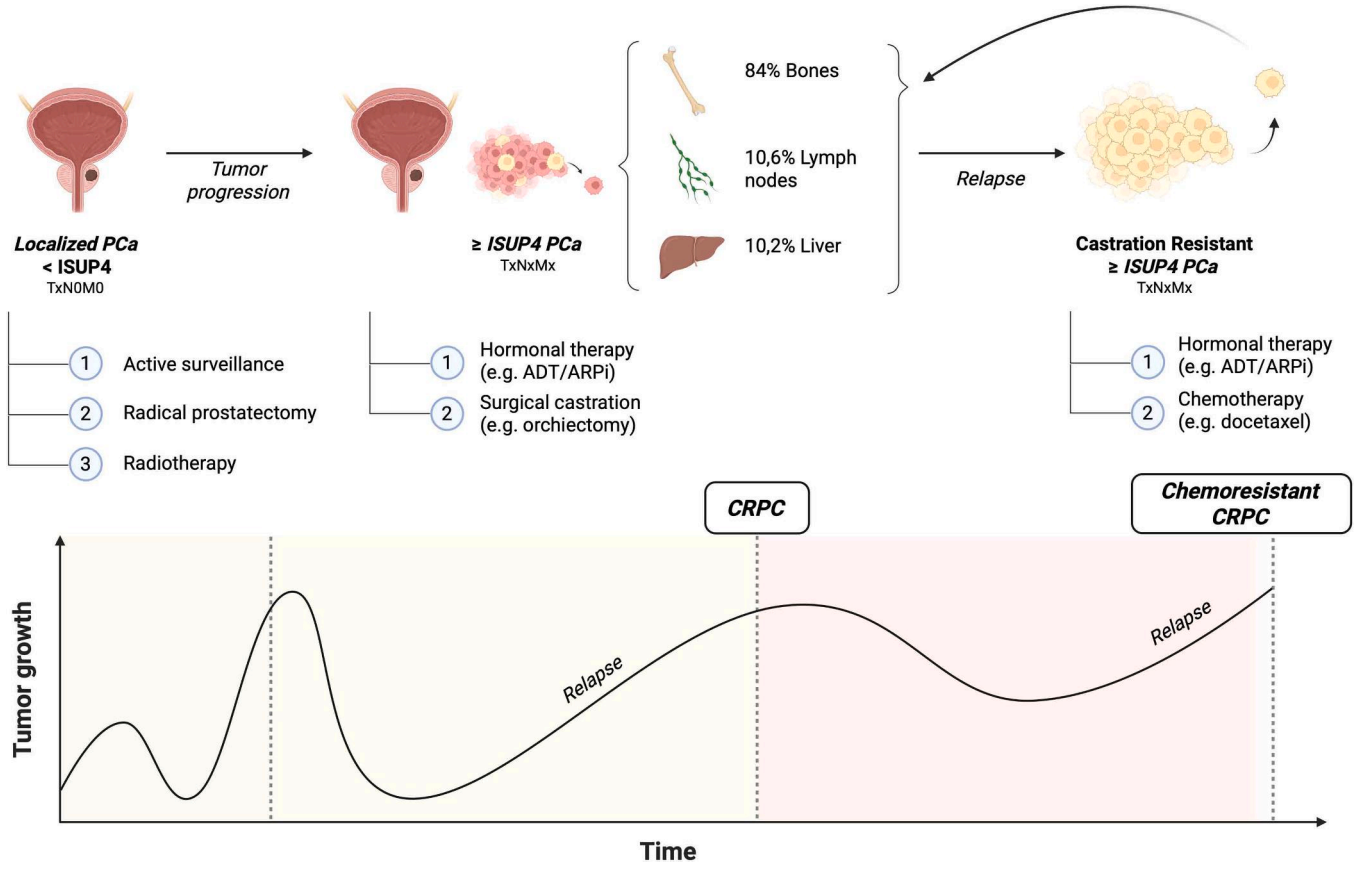

Fig. 3. Current standard of care decision tree for PCa treatment. Active surveillance is routinely proposed for patients diagnosed at an early stage with localized low-risk PCa (ISUP1/2 or T1/2N0M0). For patients with high grade localized disease (ISUP2/3 or T3/T4N0M0), curative treatment options include radical prostatectomy and/or radiotherapy. If the tumor progresses locally or beyond the prostate, or if the patient is newly diagnosed with high grade disease (ISUP4/5) or metastatic PCa, most commonly involving bone, lymph nodes or visceral organs such as the liver, the standard of care consists of hormonal therapy, achieved either surgically (e.g., orchiectomy) or pharmacologically (e.g., ADT or ARPi). Patients who relapse and progress despite castrate levels of testosterone are classified as CRPC. In this setting, the current standard treatment is chemotherapy, typically administered in combination with ADT and/or ARPIs. However, this strategy does not provide durable disease control, and no effective curative treatments are currently available once patients progress to a chemoresistant CRPC state. Created in https://BioRender.com.

xenograft models. This technique consists of grafting human cells either from *in vitro* cultured tumor cell-lines (e.g. cell line-derived xenografts) or patient biopsies (e.g. patient-derived xenografts (PDX)) into immunodeficient host mice. Although cell line-derived xenografts are convenient and reproducible, they fail to fully reflect the molecular and cellular heterogeneity seen in patients, impeding their translational relevance compared to PDX models [48]. On top of that, the success rate of tumor engraftment and growth in host mice is low (10–40%) [53,54] increasing both experimental costs and time, while patients' survival time is limited [55,56]. Finally, the low graft success rate and the absence of key modulators of tumorigenesis limit these models, making it difficult to study the interplay between immune and cancer cells.

To date, the best option to study the complex interaction between cancer cells and the TME during tumor progression is to use Genetically Engineered Mouse Models (GEMM) [57]. One of the earliest and most extensively characterized GEMMs is the Transgenic Adenocarcinoma of the Mouse Prostate (TRAMP) model, in which the SV40 large T antigen is expressed under the control of the prostate-specific probasin promoter, leading to spontaneous tumor development that progresses from PIN to adenocarcinoma within 10 weeks, and metastasis within 12 weeks [58]. Following this transgenic approach, the Knock-In Mouse Adenocarcinoma Prostate (KIMAP) model was generated by inserting the SV40 large T antigen into the prostate secretory protein 94 (PSP94) locus, thereby inducing prostate-specific tumorigenesis. However, this model has not been widely used [59]. Phosphatase and TENsin homolog (*PTEN*) gene mutations being observed in 69% of PCa and in 86% of CRPC, the majority of the currently used PCa GEMMs rely on *Pten* inactivation using the Cre-lox system [60]. This technology is derived from the recombination system of the bacteriophage P1. The Cre recombinase recognizes specific DNA sequences known as LoxP sites and catalyzes recombination between the two, resulting in the excision of the flanked sequence. To inactivate *Pten* in the prostatic epithelium, the Cre recombinase expression was under the control of tissue-selective mouse or human promoter to limit the excision to the targeted cell type/tissue [57].

Two promoters were mainly used to induce *Pten* inactivation in PECs. The first strategy uses the Cre expression under the control of the Probasin (Pb) promoter. Probasin being expressed in epithelial cells around mouse adulthood, *Pten* is inactivated during prostate maturation. Following *Pten* loss, these mice present a well-characterized PCa phenotype within 7 months. This mouse model called $PTEN^{pc-/-}$ being castration resistant, allowed for the identification of the castration resistant PECs subpopulation, called LSCmed (Lin-/Sca-1 +/CD49fmed) due to their flow cytometry profile [61,62]. Detailed analysis of this subpopulation enabled the identification of a dual-targeting strategy focusing on FOSL1/AP-1 and PIM kinases, providing a potential approach to inhibit the plastic enrichment of castration-resistant prostate cancer cells [63]. An additional strategy was based on the Cre expression under the control of the human Prostate-Specific Antigen (PSA) promoter, the controversial gold-standard PCa biomarker, to inactivate *Pten* selectively in luminal epithelial cells, believed to be the PCa progenitors. Analyses were primarily conducted in the dorsolateral

lobe (DLP) of the prostate which is presumed to be the closest anatomical and molecular counterpart to the human peripheral lobe [64], where most of the AdC are localized. However, mice with inactivated *Pten* in PECs prior the complete development of the prostate present a faster tumor progression [65], limiting the analysis of the stepwise disease progression seen in aged patients.

To overcome the limitation of the Cre activation prior to adulthood, the Cre-ER^{T2}, based on the fusion protein between the Cre and the mutated ligand-binding domain of the Estrogen Receptor (ER), was developed by Daniel Metzger and Pierre Chambon [66]. This tool allows the activation of the tissue-selective Cre strictly upon tamoxifen administration, allowing spatio-temporal control of the excision. Mice bearing biallelic *Pten* floxed and the Cre-ER^{T2} under the control of the PSA promoter was generated. Upon tamoxifen treatment at sexual maturity (e.g. 8 weeks), these mice called PTEN$^{(i)pe-/-}$ ($^{(i)}$ standing for inducible) develop PIN within 1 month, which progress to AdC within 3 months After Gene Inactivation (AGI). Almost all glands turn into AdC within 8 months AGI [64]. Few liver metastases start to appear 12 months AGI [64]. The stepwise evolution of PCa in PTEN$^{(i)pe-/-}$ mice mimics the human PCa evolution, thus making this mouse model a valuable tool for human PCa modelling.

Efforts have been made to characterize the events underlying tumor progression in PTEN$^{(i)pe-/-}$ mice. Following *Pten* loss, PECs are hyperproliferating leading to replicative stress, DNA Damage Repair (DDR) mechanisms, and p53 down-regulation by phosphorylation of both the Protein kinase B (Akt) and Mouse Double-Minute 2 (Mdm2). Afterwards, p53 is stabilized enabling p21 + /p16 + senescence entry at 3 months AGI [67]. We unraveled the presence of an early hypoxia in PECs from PTEN$^{(i)pe-/-}$ mice promoting Hypoxia Inducible Factor (HIF1a) signaling in luminal cells, a key step in the progression from PIN toward AdC [68], or from castration-sensitive toward CRPC [69]. It has also been suggested that hypoxia enhances the secretion of C-X-C motif chemokine ligand 5 (CXCL5) by PECs, thereby promoting neutrophil [also known as Myeloid-Derived Suppressor Cells (MDSC)] infiltration, resulting in an immunosuppressive phenotype. Importantly, genetic or pharmacological loss of HIF1A in PTEN$^{(i)pe-/-}$ mice reduces the immunosuppressive neutrophil infiltration in favor of effector T-lymphocytes, thus slowing down disease progression and overcoming castration resistance [68,69]. Moreover, longitudinal analysis of the tumors using droplet-based single cell transcriptomic identified distinct luminal cell states, with Luminal C1 cells being enriched in PINs, whereas the C2 state is prevalent in adenocarcinoma. Importantly, we have shown that the expression in prostatectomy biopsies of the protein encoded by the transglutaminase 2 (TGM2) gene, one of the top signature genes of luminal C2 cells, is associated with a higher risk of relapse in a cohort of 60 patients from Strasbourg University Hospital with a 10-year follow-up [68].

TP53 mutations are present in 40–50% of advanced PCa and are associated with metastatic dissemination [70]. To determine the impact of *Trp53* deficiency in *Pten*-null PECS, PTEN/p53$^{(i)pe-/-}$ mice which present more aggressive tumors than PTEN$^{(i)pe-/-}$ mice [67] have been further characterized [71,72]. The inactivation of both *Pten* and *Trp53* does not change the kinetic of senescence entry, however, the cellular state is different between PTEN$^{(i)pe-/-}$ (p21 + /p16 +) and PTEN/p53$^{(i)pe-/-}$ (p16 + only) luminal cells. The following PCa progression is faster in PTEN/p53$^{(i)pe-/-}$ than in PTEN$^{(i)pe-/-}$ mice. The aggressiveness has been highlighted both in the prostate by higher amounts of IDC and invasive carcinoma, and in the liver through the presence of micro-metastasis 6 months AGI. Multi-omic single-cell analyses revealed the emergence of a novel cell type in the prostate of those mice termed EMTc, associated with high *Cdkn2a* (p16/p19) expression, epithelial-to-mesenchymal transition signature, and enhanced Jak/Stat3 signaling. These mesenchymal features associated with Jak/Stat3 signaling is a result of an interplay between Cancer Associated Fibroblasts (CAFs) and PECs, involving Interleukin 6 (IL6), demonstrating the key role played by the stroma-cancer cells communication during aggressive PCa onset. Importantly, patients with poor outcomes exhibit higher EMTc scores, underlining the pertinence of identifying this cell type, as well as the relevance of using these GEMMs to better understand PCa progression.

Taken together, the different PCa models represent complementary tools for gaining insight into the mechanisms underlying PCa diagnosis, progression, and therapeutic responses (Fig. 4). Nevertheless, GEMM based on gene inactivation (e.g. *Pten*, *Trp53*) at adulthood seems more suitable to identify new biomarkers and treatment strategies due to the presence of TME, cancer heterogeneity, human-like histological morphologies and stepwise cancer progression.

5. Vitamin D and prostate cancer

Historically, vitamin D was the fourth in the sequence of discovery of vitamins, but was accidentally classified as a vitamin as it is essential for human health and discovered in dietary source (e.g. cod-liver oil). However, the main sources of vitamin D are the skin following ultraviolet B (UVB) exposure or the production from dietary precursors and subsequent activation in the liver and kidneys. Therefore, due to its endogenous synthesis, cholesterol-derived structure, and its function as a messenger that acts on distant target tissues, vitamin D is a seco-steroid hormone [73]. The bioactive form of vitamin D called 1,25(OH)$_2$vitamin D$_3$ (1,25D$_3$ also known as calcitriol) is produced through a cascade of hydroxylation steps in different organs. The activity of vitamin D is mediated by the vitamin D nuclear receptor (VDR) [74–76]. VDR is expressed in almost every cell type, but displays cell specific activities. 1, 25D$_3$ plays a key role in the intestine, kidney and bone for calcium and phosphate homeostasis. For decades, vitamin D deficiency and VDR loss-of-function variants were mainly associated with bone diseases (e.g.

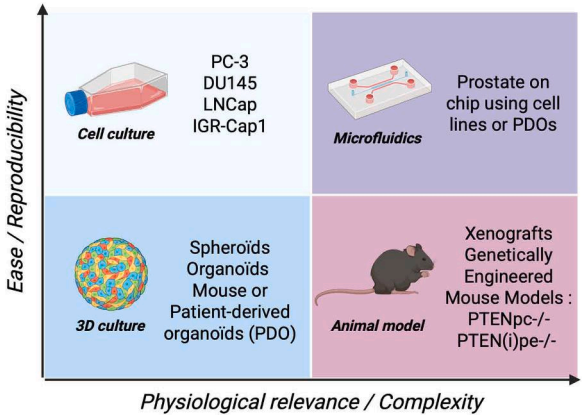

Fig. 4. Current models used to gain insight into the mechanisms underlying PCa progression or to identify new therapeutic options. 2D cell culture models, including established PCa cell lines such as PC3, DU145, LNCap, IGR-Cap1 are primarily used for high-throughput mechanistic studies and drug screening due to their simplicity, robustness and reproducibility. However, their physiological relevance remains limited. 3D spheroids, organoids and PDOs provide increased biological complexity and improved physiological relevance, although at the expense of reduced ease of use, particularly for heterogeneous PDO culture. Importantly, PDOs are currently the most suitable *in vitro* models for personalized medicine approaches, as they preserve patient-specific tumor characteristics and enable individualized therapeutic response profiling. Nevertheless, these models lack key components of the TME, which are essential for fully understanding tumor progression. To address this limitation, microfluidic devices aim to recapitulate dynamic and physiologically relevant TME interactions, enabling the study of PCa cells in contact with stromal, circulating immune or other epithelial cells under controlled flow conditions. However, these platforms remain at an early stage of development, with limited experimental validation and relatively few practical applications to date. Animal models, including xenografts and especially GEMMs currently represent the most comprehensive systems for studying PCa pathogenesis, as they closely mimic the stepwise evolution of human disease and incorporate a functional TME *in vivo*. Created in https://BioRender.com.

ricket) [77]. However, studies revealed VDR expression in tissues with no role in calcium or phosphate homeostasis, such as the prostate, and have extended the vitamin D functions toward immunity (e.g. anti-inflammatory role) [78–84], and anti-tumoral activities (e.g. anti-proliferative) [82,83,85,86–90].

Epidemiological [91,92] and in vivo [93,94] studies associate low circulating vitamin D levels to PCa progression. Recently, we confirmed in a French cohort of 77 newly diagnosed PCa patients with no calcium or vitamin D supplementation, that the levels of 25(OH)vitamin D_3, the metabolite used to determine circulating vitamin D levels, negatively correlate with those of PSA secreted by PECs, suggesting a direct impact of impaired vitamin D signaling on PECs [95]. To date, the VITAL (Vitamin D and Omega-3 Trial) clinical trial represents the largest investigation aiming to elucidate the impact of vitamin D supplementation on various cancer evolution [96]. The trial was built on 20,000 individuals all above 55 years old daily receiving for 5 years a high dose of vitamin D (2000 IU), omega 3, alone or in combination, or placebo. In this study, vitamin D showed promising effects, reducing the total cancer mortality, especially in PCa when excluding the first two years of follow-up. Yet, given the trials design (e.g. endpoint, patient selection, time of follow-up), stronger benefits for PCa may have been overlooked. In addition, *in vitro* and *in vivo* findings also indicate an anti-tumor activity of vitamin D. 1,25D_3 treatment on metastasis-derived PCa cell lines LNCaP, PC3 or DU145 suggested multiple anti-tumoral effects such as cell cycle arrest toward G0/G1 checkpoint [97,98], enhancement of apoptotic pathway through reduction of the anti-apoptotic BCL-2 expression [99–101], or even an inhibition of cell migration through higher E-cadherin expression [94,102]. Moreover, these cell lines were recently used to demonstrate that PCa in African American patients have a specific vitamin D-related genomic basis. Indeed, such high-risk PCa is driven by VDR activities alteration via the chromatin remodelers, Bromodomain Adjacent to Zinc Finger Domain 1A (BAZ1A) and SWI/SNF-related Matrix-associated Actin-dependent Regulator of Chromatin subfamily A member 5 (SMARCA5) [103]. The effects of vitamin D on proliferation and apoptosis have been confirmed *in vivo*. A high-calcium diet accelerates lesion progression and promotes tumor aggressiveness in KIMAP mice, whereas vitamin D supplementation blocks these effects by reducing calcium entry and signaling [104]. In late-stage tumors, mice in which VDR has been inactivated using the Probasin promotor exhibit hyperproliferation throughout the prostate, leading to an increasing number of filled PIN and AdC [105]. Another study brought evidence regarding the direct effect of vitamin D on cancer cell proliferation. Mice grafted with DU-145 PCa cells and fed a vitamin D deficient diet for 80 days, present a faster tumor growth than those fed with a chow diet [106]. Finally preclinical studies using the TRAMP model have examined chemopreventive effects of nutrient and hormonal interventions. Notably, treatment of TRAMP mice with vitamin D slow down early prostate tumor progression and increase the expression of differentiation markers, whereas prolonged treatment was paradoxically associated with increased distant metastasis [107]. Taken together, these evidences highlight vitamin D levels as a candidate biomarker for poor PCa outcome, and VDR downstream signaling as promising actors for prevention and slowing disease in multi-stage PCa. Nevertheless, the mechanisms by which vitamin D impacts PCa progression remains poorly understood.

6. The PTEN/VDR mouse model

A low VDR expression in PECs has been associated with PCa onset and severity [105], but the causality was not demonstrated. To challenge this hypothesis, we took advantage of mice in which we have selectively inactivated PTEN and VDR in PECs (PTEN/VDR$^{(i)pe-/-}$ mice) [95]. At 1-month AGI, these mice have a higher PEC proliferation rate compared to PTEN$^{(i)pe-/-}$ mice, demonstrating that VDR-loss promotes a faster and more aggressive PCa. RNA-sequencing (RNAseq) from isolated luminal cells of PTEN$^{(i)pe-/-}$ and PTEN/VDR$^{(i)pe-/-}$ mice showed that the expression of genes encoding proteins involved in Reactive Oxygen Species (ROS) production or in oxidative phosphorylation were enhanced in PTEN/VDR$^{(i)pe-/-}$ mice. Importantly, ROS scavenging using N-acetylcysteine (NAC) treatment reduced the proliferation rate to wild-type conditions, demonstrating that during PCa progression, VDR dampens oxidative stress to limit PECs proliferation. Whereas the tumor evolution looks similar between 3 and 9 months, prostate mass is higher and histological features more severe in PTEN/VDR$^{(i)pe-/-}$ than in PTEN$^{(i)pe-/-}$ mice 12 months AGI, highlighting the worst prognosis of PCa evolution in the absence of VDR in PECs. Moreover, metastasis was more prevalent in those same mice in comparison to PTEN$^{(i)pe-/-}$ ones. At 9 months AGI, PECs of PTEN/VDR$^{(i)pe-/-}$ mice, but not those of PTEN$^{(i)pe-/-}$, start to disseminate into the liver. The dissemination is essentially composed of immune cells (CD45 +) with less than 1% PanCK+ evasive epithelial cells. Intriguingly, we observed that the number of circulating neutrophils is associated with the extent of the dissemination. Strikingly, we show that neutrophil chemotaxis inhibition eliminates the micrometastases, suggesting the key role played by this immune subtype in the promotion of liver dissemination. These results shed light on circulating neutrophils as a new diagnosis tool, as well as a therapeutic target for aggressive PCa.

Taken together, this study gives insight into mechanisms promoting tumor progression and aggressivity (Fig. 5), as well as those underlying cell dissemination. Interestingly, the liver infiltration and the presence of rare histological subtypes in PTEN/VDR$^{(i)pe-/-}$ closely resemble those observed in PTEN/p53$^{(i)pe-/-}$ mice, in which PTEN and P53 are selectively inactivated in PECs [71,72,95], underscoring the gatekeeper played by epithelial VDR in PCa progression (Table 3).

7. Vitamin D and PCa treatment

As PCa progression and aggressivity is associated with vitamin D deficiency, the relevance of treating patients with vitamin D arises. Long-term pharmacological vitamin D supplementation in patients suffering from PCa is limited, as doses required to reach anti-tumoral effects are often associated to hypercalcemia [108–110]. Therefore, pharmaceutical industries tend to develop vitamin D analogs with enhanced anti-tumoral effects and limited pro-calcemic potency. More than 4000 vitamin D analogs have already been synthetized and some exhibited promising anti-tumoral effects (e.g. Gemini-72 [111], Xe4MeCF3 [42] or inecalcitol [112,113]).

We recently explored in PTEN$^{(i)pe-/-}$ mice the effects of Gemini-72, a vitamin D analog with more potent activities than the natural ligand [77,111]. Besides the pro-apoptotic effect on senescent PECs, this analog impedes fibroblast activation, extracellular matrix remodeling and prostatic infiltration of immunosuppressive neutrophils through CXCL5 downregulation. Together with the results obtained in PTEN/VDR$^{(i)pe-/-}$ mice, vitamin D signaling appears as a negative regulator of CXCL5 expression. Single-cell RNA-sequencing also showed that a Gemini-72 treatment induces the loss of a subset of luminal-C2 cells, underlining its impact on tumor progression. However, remaining subsets of luminal-C2 cells exhibit higher pro-survival (PI3K/AKT/mTOR) and inflammatory pathways (NF-kB), explaining limitations of vitamin-based monotherapy in PCa [111].

An expanding body of evidence has highlighted the synergistic interactions between vitamin D and several antitumor agents, including taxane-based chemotherapy, thereby enhancing their anticancer activity [112–116]. The ASCENT clinical trial investigating high-dose calcitriol (DN-101) in association with docetaxel plus prednisone, has been terminated early due to a shorter survival in the treatment arm [117]. However, these results might be due to the use of a weekly docetaxel regimen, known to be inferior to the current standard every-three-weeks schedule, thereby confounding interpretation of the vitamin D effect. Another early phase clinical studies on PCa demonstrated that inecalcitol, a low-calcemic VDR agonist, can be safely combined with standard every-three-weeks docetaxel schedule and prednisone in

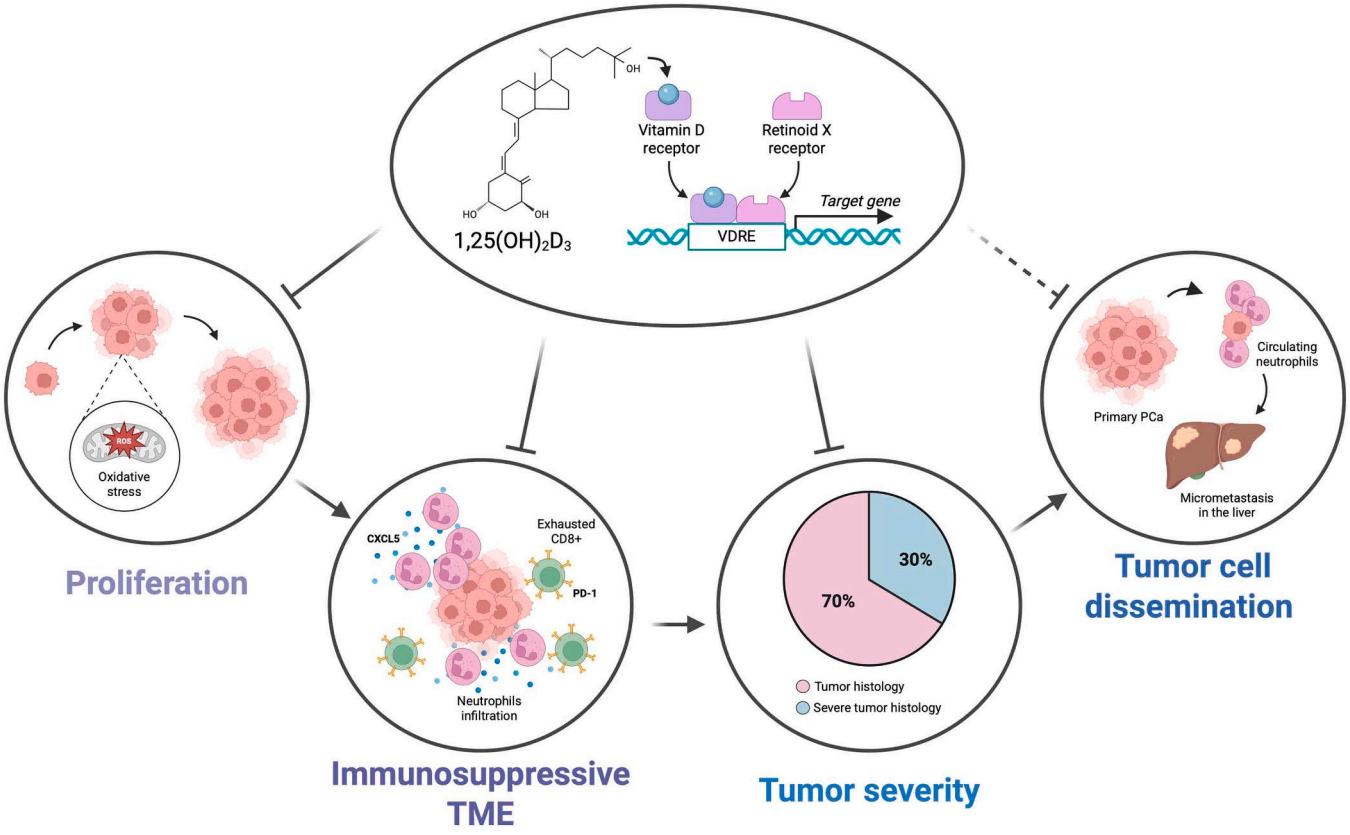

Fig. 5. Vitamin D signaling in PCa. Vitamin D (1,25D3) signaling is mediated through the genomic action of VDR. Upon 1,25D3 binding to the VDR ligand binding domain, VDR undergoes a conformational change that promotes its translocation into the nucleus, where it heterodimerizes with the Retinoid X Receptor (RXR). The resulting VDR-ligand complex functions as a transcription factor by binding to specific DNA sequences called vitamin D response elements (VDREs) to regulate the transcription of target genes. In the context of PCa, vitamin D signaling is associated to the inhibition of tumor cell proliferation and oxidative stress, processes that promote the development of aggressive tumors. By restraining excessive tumor cell proliferation, vitamin D signaling indirectly mitigates the establishment of an immunosuppressive TME. This includes limiting neutrophil recruitment driven by tumor-derived CXCL5 and reducing PD-1-expressing T-cells. Furthermore, vitamin D signaling also indirectly suppress tumor cell dissemination into the liver by impeding the accumulation of circulating neutrophils. Collectively, these findings support a protective role for vitamin D signaling in constraining tumor progression and metastatic spread. Created in https://BioRender.com.

Table 3
Summary of the GEMMs using the PSA-CRE-ER^{T2} to inactive targeted genes at adulthood. AGI: after gene inactivation induced by tamoxifen administration for 5 days.

Model	Genes	PCa progression	Model of
PTEN$^{(i)pe-/-}$	PTEN$^{flox/flox}$ (exon 4–5)	PIN: 2–3 months AGI AdC: from 3 months AGI Few liver metastasis: 12 months AGI	Primary tumor Localized PCa CRPC
PTEN/ p53$^{(i)pe-/-}$	PTEN$^{flox/flox}$ (exon 4–5) p53$^{flox/flox}$ (exon 2–10)	PIN: 2–3 months AGI Liver metastasis: 5–7 months AGI Rare tumor histologies: 5–7 months AGI	Fast evolution Metastatic PCa Aggressive & advanced tumor
PTEN/ VDR$^{(i)pe-/-}$	PTEN$^{flox/flox}$ (exon 4–5) VDR$^{flox/flox}$ (exon 2)	PIN: 1–2 months AGI AdC: from 3 months AGI Liver metastasis: 9 months AGI Rare tumor histologies: 12 months AGI	Rapid progression Aggressive & advanced tumor Metastatic PCa

mCRPC and is associated with encouraging PSA responses, supporting further evaluation of VDR-targeted therapies in this setting [112,113]. More recently, Len-Tayon and collaborators have shown that a vitamin D analog with a rigid side chain (Xe4MeCF3) used as a monotherapy had a limited effect on PCa treatment in chemoresistant IGR-Cap cells [42]. However, a Xe4MeCF3 and docetaxel co-treatment restores the chemosensitivity. Subsequently, the promising synergic effect has been tested *in vivo* on CRPC PDX. In the same way as *in vitro*, the co-treatment limits cancer growth by targeting cancer progression pathways. These results position vitamin D co-treatment as a promising strategy to enhance the efficacy of advanced PCa standard of care therapies, effectively reducing cancer progression and overcoming untreatable multi-resistance.

8. Conclusion

Through the years, the understanding of PCa has been refined and with it, appeared the need to adapt models enabling the further investigation of its complexity. GEMM represent a valuable tool for modelling the human PCa and already enabled to understand the impact of multiple factors either promoting or inhibiting cancer progression. The several mouse lines that have been established and characterized through the past 30 years allow a better understanding of the disease onset and treatment. However, pharmacological research increasingly aims for patient stratification and personalized treatments based on individual symptoms and biomarker profiles. In that end, vitamin D has arisen as a key regulator in PCa evolution. Moreover, vitamin D may offer a valuable therapeutic strategy for multi-resistant PCa. Nevertheless, further clinical investigations are needed to reconsider the use of vitamin D based therapy in PCa.

CRediT authorship contribution statement

Vanessa Friedrich: Writing – review & editing, Writing – original

draft, Visualization, Validation, Conceptualization. **Gilles Laverny:** Writing – review & editing, Writing – original draft, Validation, Supervision, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Gilles Laverny and Vanessa Friedrich report financial support was provided by INSERM. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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