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Review

Unmasking prostate cancer risk factors leveraging organoid technology

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ABSTRACT

Organoid technology is rapidly refining our understanding of organ development, physiology, and disease. The generation of patient-derived organoid cultures is paving the way for effective personalized treatments, defined based on specific genetic and molecular criteria. Moreover, the possibility of testing in vitro the response of tumor cells to the most appropriate therapeutic regimes helps to anticipate the emergence of resistance, to define the molecular mechanisms involved and, in turn, to tailor treatment through a bed-to-bench-to-bed co-clinical strategy. In addition, the creation of organoid biobank provides an opportunity to reduce the reliance on animal models, while expanding the scale and relevance of patient/human material derived analyses, ultimately accelerating the preclinical-to-clinical workflow. Prostate cancer (PCa) is one of the most common cancers in men world-wide, second only to lung cancer. Although not particularly aggressive, PCa lethality remains a clinical issue. The paucity of innovative molecular targeted therapies and the ineligibility for immunological strategies limit the clinical intervention to mainly surgery or radiotherapy for organ confined tumors, and systemic hormone therapy in the case of advanced metastatic disease. Initially effective in most patients, tumor almost inevitably relapses with palliative care remaining the only option. In this review we provide a historical and conceptual overview of organoid technology, we discuss its application in prostate cancer and outline future prospective for the development of an organoid based platform aimed at risk stratification, risk factor studies, therapeutic prediction, and personalized medicine.

1. Introduction

Organoid culture systems are built upon the intrinsic self-renewal and differentiation capacities of adult tissue progenitors. The abundance, proliferative potential and molecular definition of adult stem cells are highly tissue-dependent. While rapidly renewing epithelia such as the intestine and skin rely on active stem cell compartments, other organs display a more quiescent organization, where stem niches and progenitors are difficult to define and often emerge only under specific conditions.

Abbreviations: ISC, intestinal epithelium stem cells; RSPO, R-spondin; Lgr5, Leucine-rich repeat-containing G protein-coupled Receptor 5; SCs, Stem Cells; TA, transit-amplifying; BMP, Bone Morphogenetic Protein; TCF4, Transcription Factor 4; Dkk1, Dickkopf-1; PDGFRA, Platelet-Derived Growth Factor Receptor Alpha; ECM, extracellular matrix; UGS, urogenital sinus; UGSE, urogenital sinus epithelium; UGSM, urogenital sinus mesenchyme; TGF-b, Transforming Growth Factor-beta; FGF, Fibroblast Growth Factor; SHH, Sonic Hedgehog; Ck8, Cytokeratin-8; Ck18, Cytokeratin-18; AR, Androgen receptor; Ck5, Cytokeratin-5; Ck14, Cytokeratin-14; CHGA, chromogranin-A; SYP, synaptophysin; BPH, benign prostate hyperplasia; PCa, Prostate Cancer; GEMMs, Genetically Engineered Mouse Models; FACS, Fluorescence-Activated Cell Sorting; CARNs, Castration-Resistant Nkx3.1-expressing cells; LumA-D-L-V, Distal Luminal Cells found in the anterior (LumA), dorsal (LumD), lateral (LumL) and ventral (LumV) lobes; LumP, Proximal Luminal Cells; ASCs, adult stem cells; ESCs, embryonic stem cells; hiPSCs, human induced pluripotent stem cells; EGF, Epidermal Growth Factor; IL-22, Interleukin 22; IL10RB, Interleukin 10 Receptor Subunit Beta; IBS, inflammatory bowel disease; APC, Adenomatous Polyposis Coli; PIK3CA, Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; CRC, Colorectal cancer; PDOs, Patient-Derived Organoids; PDXOs, Patient-Derived Xenograft Organoids; DHT, dihydrotestosterone; FBS, fetal bovine serum; Alk, Anaplastic lymphoma kinase; Tak1, Transforming growth factor β-activated kinase 1; MAP3K7, Mitogen-activated protein kinase kinase kinase 7; RA, retinoic acid; ATRA, all-trans retinoic acid; RAR-gamma, Retinoic Acid Receptor gamma; Foxa1, Forkhead box A1; ERG, Ets-related gene; Pten, Phosphatase and Tensin homolog; PIN, prostatic intraneoplasia; GUPS, Genitourinary Pathology Society; ISUP, International Society of Urological Pathology; AIP, Atypical Intraductal Proliferation; IDCP, Intraductal Prostate Carcinoma; IM, Intermediate; Gsk3b, Glycogen synthase kinase-3 beta; HR, homologous recombination; BME-2, Basement Membrane Extract – Type 2; CAFs, Cancer Associated Fibroblasts; mCRPC, metastatic Castration Resistant Prostate Cancer.

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Pioneering lineage tracing studies demonstrated that in the intestinal epithelium, stem cells (ISC) reside at the base of the crypts of Lieberkühn and are characterized by the expression of the R-spondin (RSPO) receptor Lgr5 (Barker et al, 2007). Intestinal SCs maintain the intestinal epithelium through a balance of symmetric and asymmetric divisions, replenishing the stem cell pool and giving rise to transit-amplifying (TA) cells (Barker et al, 2007). These TA cells act as an intermediate population, they migrate upward and differentiate into specialized lineages, including goblet cells, enterocytes, and enteroendocrine cells (Barker et al, 2007). Upon reaching the villus tip (in the small intestine) or the surface epithelium (in the colon), these mature cells undergo anoikis and are shed into the intestinal lumen (Beumer & Clevers, 2021).

The opposing activity of Wnt and BMP signaling is crucial in sustaining the intestinal epithelium. Niche-derived Wnt ligands stabilize β-catenin inside the cells, thus allowing for the establishment of staminal programs (Sato et al, 2011; Wetering et al, 2002). Conditional ablation of β-catenin or TCF4, as well as the overexpression of the Wnt antagonist Dickkopf-1 (Dkk1), cause loss of crypt cell proliferation and aberrant crypt-villi structure of the intestine (Pinto et al, 2003; Kuhnert et al, 2004; Korinek et al, 1998; Janeckova et al, 2016). As transit-amplifying (TA) cells move towards the tip of villi, they start to differentiate thanks to the progressive increase of BMP morphogens (Haramis et al, 2004) and concomitant decrease of Wnt signaling. In particular, BMP signaling stimulates a Smad-dependent transcriptional program that counteracts stemness by repressing the Wnt signature (Auclair et al, 2007; Beumer et al, 2022) while promoting terminal differentiation of the intestinal secretory cell lineage (Qi et al, 2017). Several studies underline the critical role of BMP antagonists such as Gremlin 1, Gremlin 2 and Chordin-like 1 secreted by the subepithelial mesenchyme in establishing the correct gradient of signals that govern the homeostasis of the intestinal epithelium (Kosinski et al, 2007; Farin et al, 2012; Kabiri et al, 2014). Recently, single-cell analysis of the ISC niche identified PDGFRA^{+} stromal trophocytes and telocytes as main sources of intestinal morphogens (McCarthy et al, 2020; Kraiczy et al, 2023).

Overall, these findings highlight how the ISC niche is spatially and functionally organized to sustain a stable and readily identifiable stem cell population, providing a paradigm for tissues in which stemness is constitutive rather than inducible.

2. Prostate anatomy and organogenesis

Prostate is a gland of the male reproductive system in mammals with a blended ductal-acinar identity located underneath the bladder. Prostate gland epithelium is mainly composed of columnar luminal cells, together with basal cells that lie in direct contact with the basal lamina. In addition to the epithelial component, stromal tissue accounts for almost half of the prostate and includes fibroblasts, smooth muscle cells and the extracellular matrix (ECM) produced by these cells, being mainly collagen. Prostate main function is the production and secretion of components of the seminal fluids that help to protect and sustain sperms (Buskin et al, 2021; Prins & Putz, 2008; Vickman et al, 2020).

From a development perspective, the prostate derives from the embryonic urogenital sinus (UGS), a caudal extension of the hindgut composed by the urogenital sinus epithelium (UGSE) and the surrounding urogenital sinus mesenchyme (UGSM) (Buskin et al, 2021; Prins & Putz, 2008). The UGSE originates from the endoderm layer, which gives rise to a primitive gut tube broadly divided into fore, mid, and hindgut through the gradients of both BMP and TGF-b proteins (Sahu & Sharan, 2020; Trisno et al, 2018). The development of the hindgut continues giving rise, through various endocrine and autocrine signals, to different organs and tissues, namely the intestine, colon, bladder, penile urethra, and prostate (Sahu & Sharan, 2020). In particular, the development of the prostatic gland begins during the final phase of the embryonic life, continues through birth, and ends at sexual maturity when the increased level of circulating androgens (produced by testis) lead the gland into its mature state (Prins & Putz, 2008). Prostatic buds originate from the UGSE, expand and branch out in epithelial cords as a consequence of an intricate epithelial-mesenchymal crosstalk, which in rodents has been shown to involve multiple pathways (e.g. BMP, FGF, SHH and WNT) (Toivanen & Shen, 2017; Thomson & Marker, 2006). Progressively, canalization allows the formation of ductal lumens while epithelial cells differentiate into basal, luminal and neuroendocrine lineages (Shen & Abate-Shen, 2010). The most prominent cell population is the luminal one, characterized by its columnar polarized morphology and by the expression of markers such as Cytokeratin-8 (Ck8) and Cytokeratin-18 (Ck18), and Androgen receptor (AR) (Toivanen & Shen, 2017). Enclosing the luminal layer is the basal cell compartment, defined by reduced cytoplasm, spindle shape cell morphology, robust expression of Cytokeratin-5 (Ck5), Cytokeratin-14 (Ck14), and the ΔN-Trp63 isoform, and minimal amount of AR (Signoretti et al, 2000). Finally, rare neuroendocrine cells, whose origin and role is still poorly understood, can be identified throughout the epithelium by the expression of chromogranin-A (CHGA) and synaptophysin (SYP) (Abate-Shen & Shen, 2000; Abrahamsson, 1999; Toivanen & Shen, 2017) (Fig. 1**A-B**). It is interesting to note that AR is highly expressed in the stroma of the immature prostate, but levels decrease substantially after the gland matures (Lee et al, 2012; Xie et al, 2017) (Fig. 1**B**).

3. Adult prostate stem cells

The quiescent nature of adult prostate epithelium, together with the complex branched structure of the gland folded within the abundant stroma and anatomically differences across species has made it challenging to identify prostate stem cell niches (Toivanen & Shen, 2017). Despite human and murine prostates share the same branched structure and epithelium organization, making the mouse prostate a suitable model to translate discoveries interspecies, human and murine prostate glands differ in their gross anatomical organization. Human prostate is a uni-lobular gland characterized by three anatomically different zones – the central zone, the transition zone and the peripheral zone. A thick layer of fibromuscular stroma shields the entire anterior part of the gland. The murine prostate is composed by pairs of four distinct lobes – the anterior lobes, the ventral lobes, the dorsal lobes, and the lateral lobes. In contrast with the human prostate, mouse prostate epithelium is surrounded by a thin layer of fibromuscular stroma (McNeal, 1981; Myers, 2000; Thomson & Marker, 2006; Toivanen & Shen, 2017). These differences are not negligible. Whereas benign prostate hyperplasia (BPH) as well as prostatitis are a typical condition affecting the transition zone, likely dependent on its proximity to the urethra, human PCa usually develops in the peripheral zone. On the other hand, PCa GEMMs often show substantial differences in tumor penetrance, progression, and response to therapy in different lobes of the prostate (Ittmann et al, 2013).

Despite the differences, studying the cellular dynamics occurring in the murine prostate gland under homeostatic and stress conditions is essential for understanding the molecular mechanisms that regulate the human prostate. This will enable increasingly effective prevention and treatment of prostate diseases, which represent one of the major global health challenges (GBD 2019 Benign Prostatic Hyperplasia Collaborators, 2022).

Even though being referred to as a quiescent epithelium, early works by Evans and Chandler demonstrated that the rodent prostate is able to undergo castration cycles preserving its regenerative capacity (Evans & Chandler, 1987). Androgen deprivation reduces murine prostate size by 90% leaving small periurethral lumps consisting mostly of cells expressing basal markers (English et al, 1989, English et al., 1987), leading to the idea of a stem cell reservoir in the basal compartment. Isolation by FACS of a population of prostate basal cells (CD45^{-}CD31^{-}Ter119^{-}Sca1^{+}CD49f^{+}) within the proximal region with self-renewal potential and the ability to generate both the basal and luminal compartments of the prostatic epithelium when injected

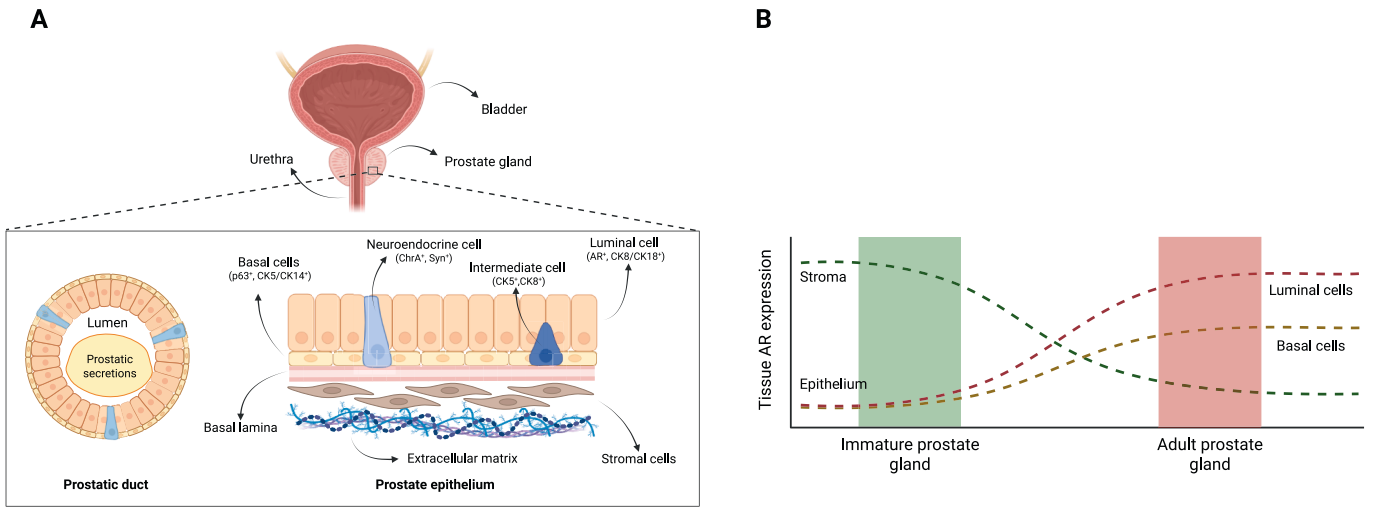


Fig. 1. Histological and molecular characteristics of human prostate epithelium. A) Prostate gland anatomy and architecture. The organization of the duct is shown at cellular and molecular levels. B) Dynamic expression of the androgen receptor in the prostatic stromal and epithelial compartment during gland development.), created in BioRender. Lunardi, A. (2026)
Adapted from (Vickman et al, 2020https://BioRender.com/gulm8x6.

subcutaneously in immune deficient recipient mice seemed to validate their hypothesis (Lawson et al, 2007, 2010). The main limitation of these results is the use of urogenital sinus mesenchyme (UGSM) to provide stromal-dependent signals. UGSM has high reprogrammable capacities as it was shown to being able to differentiate the squamous epithelium of the bladder into the secretory epithelium of the prostate (Cunha et al, 2021). Therefore, it is impossible to define whether multi-lineage capacity is intrinsic to the isolated cell population or whether it depends on the ability of UGSM to induce cellular plasticity by providing strong developmental signals that are not normally present in the adult prostate. In the same years, Shen's lab identified progenitor cells in the luminal compartment of the adult mouse prostate. Lineage tracing studies performed during prostate regeneration showed the presence of a rare castration-resistant Nkx3.1-expressing population of luminal cells (CARNs) displaying bipotentiality and self-renewal capacities (Wang et al, 2009). More recently, elaborated lineage tracing experiments performed at different postnatal timepoints tried to shed light on the presence of different stem populations in the mouse prostate (Tika et al, 2019). By tracing K14 + basal cells, Tika and colleagues demonstrated that at early stages of postnatal development basal cells represent the driving force for prostate development giving rise to all cellular lineages with some basal cells showing commitment to become luminal progenitors. During the mid-stage, multipotent basal cells were observed mostly at the tips of prostate branches participating in the expansion and development of the prostate. The existence of "intermediate" or "transit amplifying" cells, characterized by positivity to both luminal and basal markers and the ability to switch from the basal to the luminal lineage, had also been suggested by a previous work (Wang et al, 2001). Finally, after puberty, the prostate epithelium is maintained mainly by unipotent basal and luminal progenitor cells (Liu et al, 2011; Tika et al, 2019) even though the dedifferentiation of basal cells into intermediate CK5 + CK8 + cells and then into CK8 + cells may play a role in the replacement of dead luminal cells (Toivanen et al, 2016).

The precise hierarchy of the prostatic epithelium is still overall elusive and under investigation, but there are clear data pointing to the presence in the early postnatal stage of multipotent basal stem cells that shape the development of the epithelium giving rise to fully differentiated cells but also to unipotent luminal and basal progenitors which control tissue homeostasis during the adulthood (Fig. 2). Unlike the gut, where tissue homeostasis is maintained by a well-defined population of resident stem cells, the prostate appears to rely on a more flexible and context-dependent form of stemness rather than on a dedicated stem cell

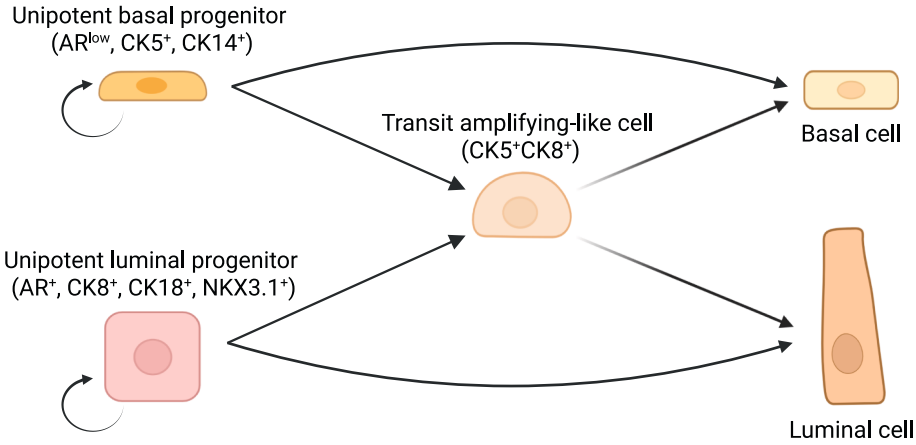


Fig. 2. Prostate stem cells in the human adult prostate epithelium. Schematically representation of stem cell hierarchy and their markers in both luminal and basal compartments, with self-renewal and differentiation capability between the two lineages.), created in BioRender. Lunardi, A. (2026)
Adapted from (Zhang et al, 2018https://BioRender.com/wi743yy.

population. In this tissue, stem-like properties can be induced in response to stimuli such as tissue damage, loss of neighboring cells, inflammation and other microenvironmental cues, which makes the unambiguous identification of a single stem cell population particularly challenging. Indeed, works using lineage tracing approaches highlighted how both basal and luminal cells could represent putative cells of origin for cancer with evidences, even though conflicting, showing that the aggressiveness could depend on the cell of onset (Goldstein et al, 2010; Lawson et al, 2010; Park et al, 2016; Stoyanova et al, 2013; Choi et al, 2012; Wang et al, 2014; Feng et al, 2025). Single-cell technologies represent powerful methodologies to dissect tissue heterogeneity and developmental processes (Luecken & Theis, 2019). Recently, these approaches have been used also in the context of human and murine prostate to study prostate development, regeneration and tumorigenesis (Henry et al, 2018; Crowley et al, 2020; Karthaus et al, 2020; Joseph et al, 2020; Crowell et al, 2019; Guo et al, 2020). Aparicio, Crowley and colleagues put effort in pooling already published datasets to create a comprehensive single-cell atlas of murine and human prostates (Aparicio et al, 2025). Interestingly, in mice they observed four luminal distal populations corresponding to the four different lobes (LumA, LumV, LumD, LumL), while luminal cells proximal to the urethra pooled all together (LumP) regardless of the lobe of origin. In humans, luminal cells split into luminal apical and luminal ductal cells resembling respectively murine luminal distal cells and luminal proximal cells. These atlases provide an essential reference framework, but their static nature and limited capacity to capture functional plasticity underscore the need for experimental systems that allow dynamic interrogation of prostate epithelial states.

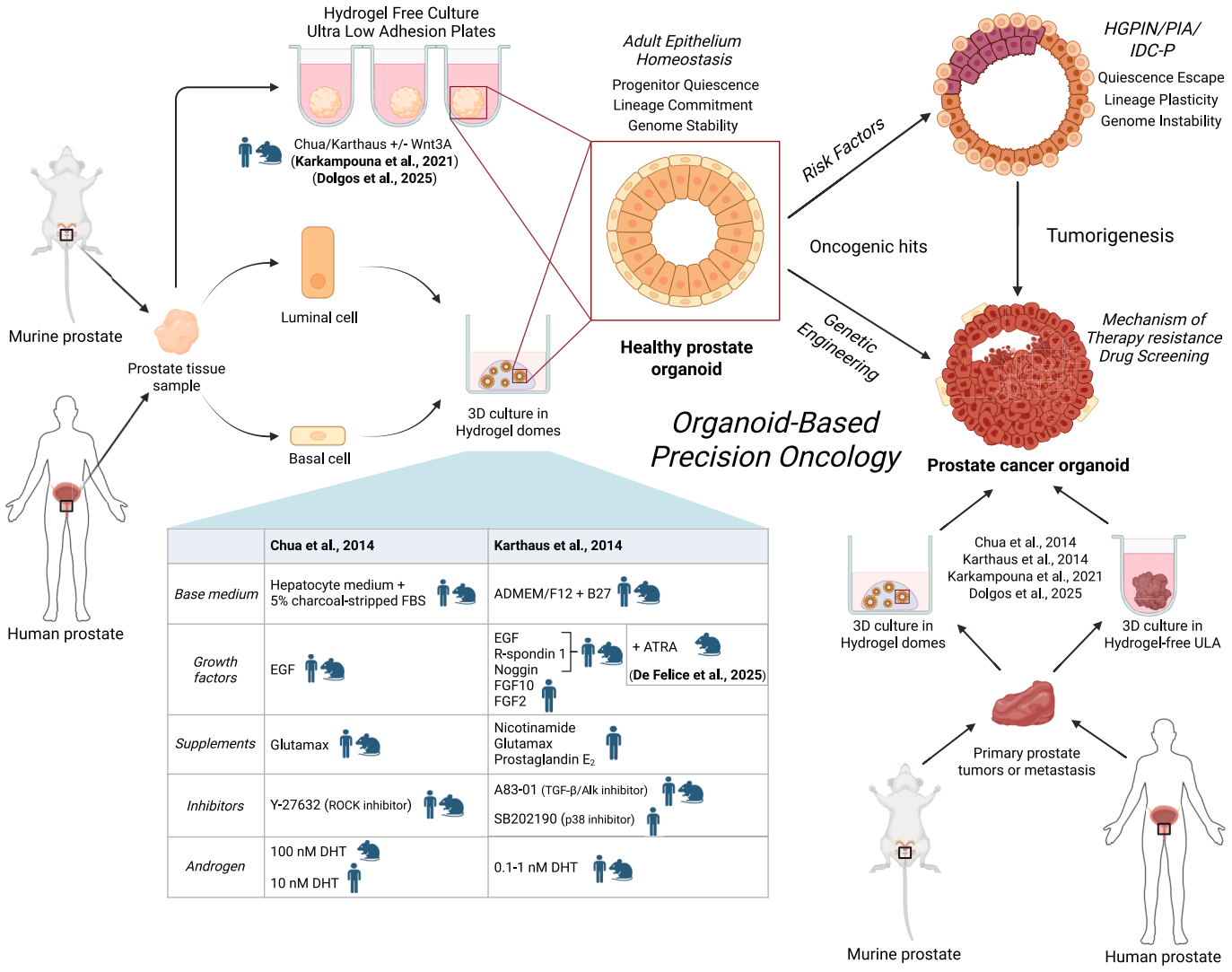
4. From tissue to organoids

Organoids are an innovative type of culture technology which allows to create in vitro complex 3D cellular systems that resemble both cellular architecture and function of the tissues of origin. Establishment of these 3D structures depends on adult stem cells (ASCs) and their self-renewal and differentiation capacity. However, other sources with different degrees of stemness can be used to generate organoids, such as embryonic stem cells (ESCs) and human induced pluripotent stem cells (hiPSCs) (Antonica et al, 2012, Antonica et al., 2017; Adams et al, 2019b; Takahashi et al, 2007). These systems can be exploited to understand organogenesis and signaling taking place in homeostatic conditions (Ciprietti et al, 2025; Yu et al, 2025). In disease relevant settings, they also allow for genetic and drug screening as well as interaction with other cellular compartments such as the immune system and stromal cells, but also interaction with microbes and pathogens (Recaldin et al, 2024; Kromann et al, 2024; Puschhof et al, 2021; Co et al, 2021). Historically, intestinal organoids were the first to be established from tissue resident adult stem cells and paved the way for the generation of complex 3D cellular systems starting from many other adult tissues. After the discovery of Lgr5 + stem cells at the bottom of colonic crypts, Sato and colleagues reported the generation of murine intestinal organoids starting from single Lgr5 + cells (Sato et al, 2009). Interestingly, these organoids display crypt-like structures organized around a void lumen. Lgr5 + cells localized at the bottom of crypts together with Paneth cells, while enterocytes, Goblet and enteroendocrine cells were found scattered through the organoid, mimicking the cellular organization of the tissue of origin. These organoids, formed in the absence of mesenchymal cells, required the culture medium to be supplemented with EGF, RSPO and Noggin, highlighting the critical role of niche-derived signals, particularly Wnt and BMP, in supporting gut crypt survival and proper epithelium differentiation (Sato et al, 2011). Then, the protocol was adapted to generate human intestinal organoids (Sato et al, 2011), opening to the possibility of studying human intestinal diseases in a sophisticated in vitro 3D setting (Fujii et al, 2016; Esposito et al, 2024; Dotti et al, 2017). Human organoids represent powerful tools to study physiological phenomena. Gut organoids, for example, were exploited to demonstrate the importance of BMP signaling for the zonation of Goblet cells, enterocytes and enteroendocrine cells along the crypt-villus axis (Beumer et al, 2022, Beumer et al., 2018). IL-22, instead, was shown to be crucial for the differentiation of Paneth cells and to produce antimicrobial peptides. Accordingly, loss-of-function mutations in the IL-22 co-receptor gene IL10RB impeded the differentiation of Paneth cells, recapitulating features observed in certain hereditary forms of inflammatory bowel disease (IBS) (He et al, 2022). Along with studies focusing on adult tissue homeostasis, the combination of gut organoid technology with CRISPR/Cas9 genomic engineering methodology provided an unprecedented asset for modelling and studying the role of precise molecular aberrations in colorectal cancer onset (Drost et al, 2017) and progression (Drost et al, 2015; Matano et al, 2015). Exploiting CRISPR/Cas9 approach, Drost and colleagues and Matano and colleagues demonstrated that human adult intestinal stem cells with combined loss of *APC* and *P53* genes generate intestinal organoids characterized by genomic instability (massive aneuploidy), a prerequisite for cellular transformation. Additional mutations of *KRAS* and/or *PIK3CA* genes and *SMAD4* loss of function in the APC/P53-defective cellular context allowed human intestinal organoids to grow in the absence of stimuli and generate aggressive colorectal tumors following xenotransplantation into immunocompromised mice. Interestingly, orthotopic transplantation of human colonic organoids into the intestinal epithelium of immune-deficient mice allowed for the first time to study the human colon epithelium, and human CRC initiation, directly in the colonic environment (Fumagalli et al, 2017; Sugimoto et al, 2018). In parallel, the establishment of organoid lines from patients derived colorectal cancer samples (PDOs) and mouse xenografts (PDXOs) have led to the identification of specific molecular signatures associated with tumor response to standard therapies and paved the way for more effective rationalized targeted treatments (Arena et al, 2020; Durinikova et al, 2022; Mauri et al, 2021).

5. Prostate organoids

Building on these advances, cultivation of organoids was successfully adapted to model other human tissues, such as stomach (Bartfeld et al, 2015), liver (Huch et al, 2015; Broutier et al, 2017), breast (Dekkers et al, 2021), ovary (Hill et al, 2018; de Witte et al, 2020), bladder (Minoli et al, 2023) including the prostate (Gao et al, 2014; Karthaus et al, 2014; Karkampouna et al, 2021).

Within the prostate field, several groups had previously reported the generation of *prostaspheres* from murine prostate epithelial cells. These 3D structures exhibited self-renewal capacity, indicating the presence of stem/progenitor cell populations, yet they were predominantly composed of $CK5^{+}$ basal cells and lacked a well-defined luminal compartment (Xin et al, 2005; Shi et al, 2007). Importantly, the culture conditions did not support the long-term growth of human prostatospheres (Wang et al, 2018). In 2014, the groups of Michael Shen, Charles Sawyers and Hans Clevers reported the successful generation of prostate organoids starting from both human and murine adult primary tissue (Fig. 3) (Karthaus et al, 2014; Chua et al, 2014). In both studies, organoids were grown in an ECM-enriched scaffold (Matrigel®) and included dihydrotestosterone (DHT) supplementation, reflecting the androgen dependence of prostate tissue. Whereas Karthaus and colleagues used the media originally developed for intestinal organoids, Chua and colleagues adopted a hepatocyte culture medium supplemented with low levels of fetal bovine serum (FBS) (Fig. 3). In both works, prostate organoids were derived from single basal or luminal cells, supporting the existence of bipotent progenitor cells in both epithelial compartments. However, prostate organoids derived from luminal cells better recapitulate key features of prostate tissue, displaying a multilayer epithelial architecture and the ability to form glandular structures when recombined with UGSM and transplanted under the kidney capsule of recipient mice. Moreover, both works described the establishment of PCa organoids via the genetic manipulation of wild type prostate



	Chua et al., 2014	Karthaus et al., 2014
Base medium	Hepatocyte medium + 5% charcoal-stripped FBS	ADMEM/F12 + B27
Growth factors	EGF	EGF, R-spondin 1, Noggin, FGF10, FGF2 + ATRA (De Felice et al., 2025)
Supplements	Glutamax	Nicotinamide, Glutamax, Prostaglandin E_2
Inhibitors	Y-27632 (ROCK inhibitor)	A83-01 (TGF-β/Alk inhibitor), SB202190 (p38 inhibitor)
Androgen	100 nM DHT, 10 nM DHT	0.1-1 nM DHT

Fig. 3. Organoid-Based Precision Oncology. Healthy prostate organoids can be generated starting from both murine and human adult prostates. After tissue dissociation single luminal and basal cells seeded in an ECM-rich environment or in ultra-low adhesion plates and cultured under defined media conditions generate organoids containing both luminal and basal cells, faithfully recapitulating the 3D architecture and functional properties of the prostate epithelium. Prostate cancer organoids can be similarly obtained by fresh tumoral tissue or by introducing risk factors or oncogenic alterations into wild-type prostate organoids. Created in BioRender. Lunardi, A. (2026) https://BioRender.com/dy8zb5p.

organoids or the derivation from prostate tumor samples collected from PCa GEMMs, establishing the conditions for many other investigations (Steiner et al, 2023; Chan et al, 2022; Zhang et al, 2020; Romero et al, 2024; Eyunni et al, 2025; Li et al, 2026). In the same year, Gao and colleagues reported the establishment of human PCa organoid lines from metastatic biopsy specimens (Gao et al, 2014). PCa organoids reproduce the genetic aberrations and copy number variations characteristic of human prostate tumors, highlighting their value as physiologically relevant models for prostate cancer research (Rodrigues Sousa et al, 2025) and drug screening aimed at identifying personalised strategies of precision medicine (Karkampouna et al, 2021; Kang et al, 2025; Guo et al, 2023; Tang et al, 2022; Li et al, 2026). There have been no major improvements in the composition of culture media or the factors used for the formation of prostate organoids under ECM-rich conditions, with the exception of the study by De Felice and colleagues, in which the addition of ATRA substantially improves luminal differentiation and the formation of large hollow organoids (De Felice et al, 2025) (Fig. 3). Of note, hydrogel-free protocols were among the first to be adopted historically, although the cells were used to form spheroids rather than true organoids (Shi et al, 2007; Lawson et al, 2007). These models utilize ultra-low adhesion (ULA) plates to promote 3D cell aggregates. Recent studies, however, have demonstrated that it is possible to successfully obtain organoids derived from prostate cancer patients using ULA plates with a dedicated culture medium, namely a cocktail based on the two classical recipes by Chua and Karthaus with or without the addition of Wnt3a (Karkampouna et al, 2021; Dolgos et al, 2025) (Fig. 3). Overall, prostate organoids represent a major improvement in pre-clinical and clinical research on prostate diseases. While protocols for murine prostate organoids allow the generation of stable lines that can be maintained over time, protocols for the generation of human prostate organoids are not as effective. Both healthy and cancerous human prostate organoids survive only a few passages in vitro, suggesting a rapid loss of fitness. Under such conditions, it can be difficult to study tumor biology and even more challenging to interpret the efficacy of specific therapeutic treatments.

6. Prostate organoids to decipher age-related cancer risk factors

In the past two decades, the effort dedicated by the scientific community to establishing and studying human and mouse tumor-derived

organoids (*alias* patient-derived organoids PDOs, tumoroids) has grown exponentially (Tuveson & Clevers, 2019; Yang et al, 2023). PDOs and tumoroids have been successfully exploited to define the role of cancer-associated mutations, to identify mechanisms of therapy resistance, as well as to test innovative and accurate therapeutic strategies (Kondo & Inoue, 2019; Bleijs et al, 2019). Vice versa, minimal attention has been paid to study wild type organoids derived from adult healthy tissues, which however may have a substantial impact in oncology helping to disentangle crucial molecular events contributing to disease onset.

The pick of incidence of newly diagnosed PCa in men over 60, clearly indicates aging as the most relevant risk factor (Huynh-Le et al, 2020; Chen et al, 2024). Aging is a multi-layered biological process which combines concomitant detrimental changes at both molecular, cellular, and systemic scale. Definition of molecular circuits governing the homeostasis of adult tissue progenitors can shed the light on cell-autonomous and nonautonomous pathways whose weakening during aging might contribute to aberrant proliferation, genome instability, or reduced lineage constrain, which are all well-established tumor risk factors.

In this scenario, a recent work from Lunardi's lab demonstrates the autocrine/paracrine function of Activin A in safeguarding quiescence of adult prostate progenitors (Cambuli et al, 2022). Binding of Activin-A to Alk receptors triggers the Smad-independent non-canonical Tgf-beta pathway, whose key players Tak1 and p38 kinases stabilize p21 protein and promote the nuclear shuttling of both cell cycle inhibitors p21 and p16. However, adult prostate progenitors escape quiescence spontaneously after months of continuous culture by lowering the production and secretion of Activin A. Interestingly, the reduced amount of p21 and p16, no more sufficient to maintain cellular quiescence, are very likely enough to partially contrast the Egf signaling on the replication forks, thus determining a condition of replicative stress in adult prostate progenitors. Activin A-adapted organoids grow slower than controls, they show evident signs of genomic instability (e.g., telomeres instability, tetraploidy, aneuploidy) and generate highly proliferative dysplastic lesions when orthotopically transplanted in the prostate of adult syngeneic recipient mice. Although measuring the amount of Activin A within the prostate is currently unrealistic, the identification of the TAK1/p38 non-canonical TGF-β pathway as a pivotal factor in safeguarding the quiescent state of adult prostate progenitor cells may have shed light on the reason for the recurrent loss of the *MAP3K7* gene in human PCa (Wu et al, 2012; Liu et al, 2007; Kluth et al, 2013; Jillson et al, 2021). More recently, the same group has defined a major role of Vitamin A in the definition of the luminal compartment of mouse prostate organoids (De Felice et al, 2025). Adult prostate progenitors convert Vitamin A in retinoic acid (RA) who's binding to RAR-gamma promotes the expression of the luminal pioneering factor Foxa1. Foxa1 controls the expression of hundreds of genes by binding both proximal (promoters) and distal (enhancers) regulatory elements along the genome included those of several luminal progenitor-restricted genes. Moreover, it shapes the activity of the Androgen Receptor (AR) by substantially redefining its distribution on the genome. Concomitant RA and androgen signaling are essential to establish and maintain the luminal lineage as well as to assemble a functional luminal compartment in the mouse prostate. Mutant forms of FOXA1 commonly identified in both breast and prostate cancer have been associated to gain-of-function activity of the transcription factor (Adams et al, 2019a; Arruabarrena-Aristorena et al, 2020). More recently, prostate organoids have suggested a more heterogeneous picture of the oncogenic activities associated with different classes of FOXA1 mutations (De Felice et al, 2025), a finding later confirmed by several other studies (Ladewig et al, 2026; Eyunni et al, 2025). Notably, several clinical studies reported positive association between increasing amount of plasma retinol and prostate cancer risk (Loh et al, 2023; Key et al, 2015). Overall, these two works underline the value of wild type organoids as a sophisticated model to define pathways essential for the homeostasis of the adult progenitor compartment of the prostate. Aging-dependent reduction of Activin A/TAK1 signaling in adult prostate progenitor cells may trigger an abnormal exit from the quiescent state and lead to genomic instability. Concurrently, abnormal intake, absorption, or metabolism of vitamin A, leading to deregulation of retinoic acid (RA) signaling in presence of somatic FOXA1 mutations could disrupt proper commitment to the luminal lineage and promote cellular plasticity. These events clearly expose the prostate epithelium to the risk of neoplastic transformation. A further critical setting where wild type prostate organoids can be exploited to is the definition of the pro-tumorigenic role of non-oncogenic molecular aberrations characterizing pre-malignant prostate lesions. Among them, one the most interesting is undoubtedly the Chr21q22 genomic rearrangement (Tmprss2-ERG) determining the de novo expression of the N-terminal truncated (Met 40) version of the transcription factor Ets-related gene (ERG) (Tomlins et al, 2005; Abida et al, 2019; Wang et al, 2006).Characterizing almost half of human PCa ERG is a highly studied gene whose functions in PCa are mainly associated with epithelial-to-mesenchymal transition, tumor progression and resistance to therapy (Leshem et al, 2011; Tomlins et al, 2008; Mao et al, 2019; Galletti et al, 2014; Rickman et al, 2010). Although still debated, mouse studies suggest that ERG expression is not sufficient per se to drives PCa, but it promotes tumor progression and aggressiveness if combined to other molecular aberration such as the loss of Pten (Lorenzoni et al, 2022; Shao et al, 2018). Unexpectedly, different groups report the expression of ERG in prostatic intraneoplasia (PIN) lesions of the gland. While PIN is generally not considered a precursor of PCa, ERG + PIN frequently is (Gao et al, 2012; Park et al, 2014) thus suggesting a pro-tumorigenic role of ERG. Studies on ERG function in premalignant states of the prostate have gained even greater clinical relevance following the release of new guidelines by the Genitourinary Pathology Society (GUPS) and the International Society of Urological Pathology (ISUP), which identify ERG expression as a crucial biomarker for diagnosing atypical intraductal proliferation (AIP) and intraductal prostate carcinoma (IDCP) (Shah et al, 2026). Along this line, lineage tracing experiments have identified ERG's tumor-initiating activity in a specific population of prostate basal cells that also express luminal genes ($Basal^{Lum}$), rather than in the broader population of ERG-positive luminal cells. ERG expression in $Basal^{Lum}$ cells leads to intermediate (IM) cells with stem cell features included the expression of basal, luminal, hillock, and club marker genes, prior to the transition to Krt8-positive luminal cells (Feng et al, 2025). Genetically engineered mouse prostate organoids expressing ERG Met40 under the control of doxycycline highlighted several underappreciated functions of ERG in healthy adult prostate progenitors (Lorenzoni et al, 2022). ERG + adult prostate progenitors survive, grow and form organoids in the absence of essential growth factors (e.g., Egf), while wild type dye. ERG + adult prostate progenitors are more prone to differentiate into the luminal lineage than the basal one. Finally, by repressing Wnt4 signaling, expression of ERG if combined with a reduction of R-spondin from the stroma promotes the Gsk3b-dependent degradation of Nkx3.1 in adult prostate progenitors. Loss of Nkx3.1 protein limits the efficiency of the homologous recombination (HR) pathway (Zhang et al, 2016; Bowen et al, 2013) and favors a condition of genomic instability through the accumulation of unrepaired double-strand breaks. In so doing, ERG provides adult prostate progenitors with the ability to grow in the absence of stimuli while in parallel harnessing the stability of their genome, a direct route to neoplastic transformation.

The value of organoid technology in studying early events associated with cancer onset was also demonstrated by Dost and colleagues, who exploited lung organoids to define the pleiotropic role of oncogenic KRAS in lung tumorigenesis (Dost et al, 2020).

7. Conclusion and future perspective

In conclusion, organoid technology represents an interesting tool for addressing various biological questions that are still awaiting answers. Undoubtedly, thanks to their use, we are deepening our knowledge of

the mechanisms and pathways that regulate adult progenitor homeostasis, identifying possible risk factors and perhaps even approaching the molecular principles of ageing. Nevertheless, prostate organoids are still far from being a well-established tool and from replicating several key features of the adult prostate. Patient-derived organoids (PDOs) survive in vitro for only a few passages, which significantly limits the experimental procedures that can be performed and the ability to conduct independent biological replicates that is essential to test the robustness of the results. Some improvements have been obtained by growing human PDOs in suspension in ultra-low adhesion plates instead of using hydrogels like Matrigel® or BME-2 (Karkampouna et al, 2021; Dolgos et al, 2025). Furthermore, they are composed almost exclusively of epithelial cells – primarily basal cells- and thus lack key components of the stroma, such as fibroblasts, endothelial cells, and immune cells. Mouse prostate organoids are much more stable than human ones and can be maintained in Matrigel® with the appropriate factors for an indefinite number of passages (Cambuli et al., 2022). It is important to note that retinoic acid signaling can generate a more pronounced luminal compartment and substantially promotes lumenogenesis in mouse prostate organoids (De Felice et al., 2025). However, just like human prostate organoids, mouse prostate organoids also have a homogeneous epithelial structure that does not replicate the abundant connective tissue typical of the prostate gland, which obviously constrains their scientific value. The development of heterotypic organoid cultures known as assembloids is necessary to bring the complexity of the organoid model even closer to that of the tissue of origin, thereby improving its accuracy and predictability (Iachini et al, 2025; Onesto et al, 2024; Sharpe et al, 2024; Rossi et al, 2018). Prostate cancer (PCa) assembloids were recently developed by Lee and colleagues by combining PDOs with corresponding cancer-associated fibroblasts (CAFs) derived from the same tumor samples (Lee et al, 2025) Two lines of PCa assembloids were generated from a hormone naïve localized PCa and from a castration-resistant metastatic prostate cancer (mCRPC) by combining PDOs and corresponding CAFs. In addition to an increase in the number of Ki67 + proliferating cells, the assembloids proved significantly more resistant to treatment with enzalutamide or docetaxel, clearly demonstrating the importance of modeling cellular complexity −whether studying healthy tissue or tumors- to improve the reliability of in vitro 3D avatars.

CRediT authorship contribution statement

Marta Cantarelli: Writing – review & editing, Writing – origi, nal draft, Data curation. **Elisa Marmocchi:** Writing – review & editing, Data curation. **Andrea Lunardi:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Rubens Begaj:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

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Declaration of competing interest

The authors 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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Data availability

No data was used for the research described in the article.

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