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Review Article

Apparent Differences in Prostate Zones: Susceptibility to Prostate Cancer and Benign Prostatic Hyperplasia

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ABSTRACT

Men are inevitably plagued by prostate disease throughout their lives. However, the understanding of the pathogenesis of prostate diseases is still limited. In the 1960s, McNeal proposed the theory of prostate zones. The prostate was divided into three main zones: Transition zone, central zone, and peripheral zone. Over the past 50 years, significant differences between different prostate zones have been gradually revealed. We summarized the most significant differences in different zones of the prostate. For the first time, we proposed the "apparent difference in prostate zones" concept. This new concept has been proposed to understand the different zones of the prostate better. It also provided new ideas for exploring the susceptibility of lesions in different prostate zones. Despite the reported differences between zones, the treatment of prostate-related diseases remains partition agnostic. Therefore, we also discussed the clinical significance of the "apparent difference in the prostate zone" and emphasized the necessity of prostate zones.

Keywords: Prostate; Transition zone; Central zone; Peripheral zone; Apparent differences

INTRODUCTION

The prostate is a modern anatomical organ, a unique gonadal organ for men. It is located between the bladder and the urogenital diaphragm. The prostate gland encapsulates the bladder neck [1]. It is inevitable for men to be affected by prostate disease in their lives. At the same time, with the advent of the era of severe global ageing, the incidence of prostate-related diseases has increased significantly. This has become a significant problem affecting middle-aged and older men's health and quality of life. Among them, Benign Prostatic Hyperplasia (BPH) and Prostate Cancer (PCa) are the most common lesions occurring in the prostate. The occurrence of BPH is almost inevitable during a man's lifetime. BPH is one of the most common chronic progressive diseases causing abnormal urination in middle-aged and older men. The clinical symptoms of BPH were not evident at the beginning. With the progression of the disease, the Lower Urinary Tract Symptoms (LUTS) caused by it seriously bother older men [2,3]. A small number of men may remain asymptomatic for life. These men are referred to as "histological BPH" only. It has not progressed to "clinical BPH". The probability of prostate-related diseases increases with age. Epidemiological data show that when men reach the age of 60, the probability of developing clinical BPH reaches 50%. When men are 85 or older, this probability rises to 90% [4]. BPH is the most common lesion occurring in the transition zone of the prostate. The most common lesion occurring in the peripheral region is PCa. According to the latest cancer data, PCa ranks first in new cancers and is the third most common malignant tumour in men [5,6].

In the 1960s, the zonal anatomy theory of the prostate proposed by McNeal was widely used by clinicians [7]. For more than half a century, it has been increasingly clear that PCa mainly occurs in the Peripheral Zone (PZ), BPH mainly occurs in the Transition Zone (TZ), and the Central Zone (CZ) is rarely involved by cancer or hyperplasia [8]. Moreover, PCa in the PZ had a higher malignant potential and worse clinical outcomes than in the TZ group. "Based on this fact, we speculated that the marked variability in the different prostate regions induces

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disease susceptibility." Therefore, understanding the pathological changes of the prostate from the perspective of prostate compartmentalization may reveal the critical pathogenesis. In this work, we described in detail the process of understanding the anatomy of the prostate; in addition, the concept of "Apparent difference in prostate zones" was first proposed. This new concept contributed to a better understanding of the different divisions of the prostate. Meanwhile, we summarized the development process of the prostate in a timeline and attempted to explain these differences from the perspective of embryonic origin. In addition, we discussed the regulatory role of sex hormones in the physiological and pathological processes of the prostate. We focused on the role of sex hormones and their receptors in prostate development. Finally, we discussed the clinical significance of the above information for prostate diseases and clarified the necessity of prostate regional diagnosis and treatment.

EVOLUTION OF THE PROSTATE ZONES

Historical evolution of prostate zones

The prostate is the most significant substantive organ in the male accessory gonad. The understanding of the anatomy of the prostate has undergone three necessary historical evolutions. In 1912, Lowsley, in a study of the embryonic development of the prostate, observed that epithelial buds emanate from the urogenital sinus in determined pairs [9]. Furthermore, five separate groups of prostatic ducts identified by Lowsley are called "lobes". Therefore, Lowsley proposed the earliest anatomical prostate lobulation method, dividing the prostate into anterior, middle, posterior and lateral lobes. Lowsley determined the average number of conduits in each lobe: The lateral lobe had the most significant number of conduits, followed by the middle and posterior lobes. The posterior lobe occurred in the prostatic urethra distal to the opening of the ejaculatory duct-epithelial buds of bilateral lobes branch on both sides of the verumontanum. The middle lobe duct originated from the posterior urethra proximal to the opening of the ejaculatory duct. Epithelial buds of the anterior lobe branch anteriorly to the verumontanum. The anterior lobe was most pronounced before the 16th week of embryogenesis and began to degenerate after the 22nd week. The spatial relationship of catheter origin from the urethra was obscured by the complexity of the catheter branches, particularly at the site where the posterior and middle lobes merge. Based on these earlier studies, it was known that the five lobes of the prostate have different origins during the embryonic period and gradually fuse to form the main gland of the prostate after birth. In adults, however, such lobes become no longer discernible [10].

Franks proposed the prostate hormone sensitivity dichotomy in the 1950s. He divided the prostate into two parts, the inner gland and the outer gland, based on the differences in the sensitivity of the glands to sex hormones. The inner gland was partially composed of the inner mucosal and submucosal glands, which appear as hypoechoic areas on ultrasound. The outer gland was mainly composed of long branched glands, which appear as a solid echogenic area under ultrasound. Franks suggested that the inner gland was sensitive to both androgens and estrogens and was the most common area of BPH [11]. The outer gland was only sensitive to androgens and was the most common area of PCa. This method was gradually used less because it has yet to fully meet the needs of the development of medical imaging in recent years.

In the 1960s and after, McNeal proposed the widely used theory of prostate zones based on histology, protein expression, imaging, clinical features, and other aspects [7,12-16]. The zonal anatomy model of the prostate developed by McNeal had replaced the earlier models [9,11]. McNeal first divided the prostate into glandular and non-glandular parts according to histological type. The non-glandular tissue, anatomically called Anterior Fibromuscular Stroma (AFMS), was composed of muscle tissue extending downward from the detrusor muscle of the bladder neck and upward from the striated muscle of the membranous urethra. The glandular tissue is the main component of the prostate and the part of the prostate that functions. According to the different structures around the prostate, the glandular tissue of the prostate was further divided into three zones: Transition Zone (TZ), Central Zone (CZ), and Peripheral Zone (PZ). TZ accounted for 10% of the glandular tissue, CZ 20%, and PZ 70%.

McNeal prostate zones theory

It is easiest to describe the divisions of the prostate using the urethra and ejaculatory duct as anatomical landmarks. The proximal urethra goes obverse, and the distal urethra goes parallel. The lengths of the proximal urethra and distal urethra were 1.5 cm each. With the verumontanum as the boundary, the proximal urethra and the distal urethra formed an Angle of 35°, accompanied by the ejaculatory ducts running parallel on both sides [17]. TZ is located in the proximal urethra of the prostate and is symmetrically distributed on both sides of the proximal urethra. Almost all cases of BPH occur in the TZ region. The CZ is located at the base of the prostate and Narrows at the verumontanum. Thus, CZ has a pyramidal or conical shape. The CZ encloses the ejaculatory duct and the seminal vesicle duct. In other words, the ejaculatory duct and seminal vesicle duct pass through CZ.

The volume of CZ is significantly larger than that of TZ, but the probability of onset is very low. The PZ is the largest of the three zones by volume, accounting for 70% of the glandular tissue of the prostate and constituting the rest of the gland. PZ included the outer, dorsal, and apical surfaces of the prostate. The PZ encompassed most of the CZ, extended caudally, and encompassed the distal portion of the urethra. The PZ is mainly adjacent to the AFMS. AFMS account for 33% of the total prostate volume and consist of fibrous and smooth muscle matrix. As it is named, the AFMS has no glandular component and constitutes the anterior surface portion of the prostate. Furthermore, based on anatomical histological similarities, McNeal considered the middle lobe to be equivalent to his description of CZ and the two lateral and posterior lobes together to be equivalent to PZ [18]. After that, Lee et al., further

clearly illustrated the concept of compartmental anatomy of the prostate in a 3D schematic model [19].

The prostatic zone is dynamic

The total volume of the prostate increases by an average of 2.5% per year with age. The prostate is a sex hormone-dependent organ, and the prostatic zone shows dynamic changes in response to changes in testosterone secretion. During the neonatal period and adolescence, the prostate volume shows two periods of rapid growth, which are mainly due to androgen exposure and belong to physiological enlargement [20]. After the age of 45, the prostate begins to enter the accelerated phase of volume growth again. This phenomenon belongs to pathological enlargement. In the elderly, the prostate volume is still further increased after androgen reduction. There is no clear molecular evidence for why BPH occurs when androgen levels decline in older men. Previous studies have initially suggested a significant positive correlation between age and serum estrone concentration on changes in TZ volume [21]. This may be related to the imbalance of hormone levels in the body, the high expression of Dihydrotestosterone (DHT, and the release of cytokines. Physiological and pathological factors make the volume ratio of different prostate zones dynamic. The most typical manifestation of this change is the change in the volume of TZ in the prostate [22]. After the completion of prostate development in adolescence, the volume of TZ stabilizes at 5%-10% of the total prostate volume. After age 35, the volume of CZ gradually decreases, and the increase of TZ causes a large part of the reason, and then the compression of CZ. With ageing or the influence of BPH, TZ volume can expand to 30% of the total prostate volume by the age of 60 years in men [21]. In addition, a recent study showed a significant correlation between prostate growth rate and body mass index. The volume of PZ increased most rapidly between the ages of 60 and 70, whereas the volume of TZ increased constantly across all ages [23]. However, contrary to this conclusion, an earlier study suggested that prostate growth before the age of 50 may be mainly due to the enlargement of the PZ; however, after the age of 50 years, the increase in prostate volume was mainly due to the enlargement of TZ [24]. We hold that the differences in conclusions between the two studies may be limited by the different imaging assessments used. MRI has apparent advantages in the evaluation of different regions of the prostate. Despite the current understanding that prostate zones are dynamic, the growth pattern of different prostate regions remains largely unknown.

SIGNIFICANT VARIABILITY BETWEEN PROSTATE ZONES

Differences in clinical characteristics

McNeal prostate zones theory has been widely used and demonstrated since it was proposed. The differences in pathogenesis, histological features, biological behaviour and malignant potential among different prostate regions have been gradually revealed [25,26]. The three glandular zones that the prostate contains (TZ,CZ,PZ) varied greatly in their susceptibility to cancer and hyperplasia. TZ was the most common zone of BPH, and almost all cases of BPH occur in this zone. However, the incidence of PCa in TZ was low: Data show that about 10%-20% of PCa occur in TZ [27,28]. In contrast, PCa was highly prevalent in PZ. The incidence of PCa in PZ was 70%-90% [29]. CZ is rarely invaded by carcinoma or hyperplasia [30]. Worldwide, only a few studies have reported carcinogenesis in CZ. Meanwhile, different prostate regions' biological behaviour and malignant potential were also different [28,31]. PCa located in PZ had higher malignant potential and worse clinical outcomes [32,33]. Tumors generated in the PZ showed increased biological activity and aggressiveness compared to TZ [33]. Moreover, PZ carcinogenesis was more frequently associated with prostatic intraepithelial neoplasia [34]. In addition, epithelial proliferation and apoptosis were altered in the compartmental structure of the prostate during prostate development. This was mainly reflected by the fact that TZ's cell proliferation and apoptosis rates were less than those of PZ. TZ had a more substantial anti-apoptotic effect than PZ [28,35]. In another review, we summarized and described the differences in PCa between PZ and TZ. There, we gave more precise evidence [36,37].

Differences in histology

The glandular tissue in different prostate zones contains a variable number of tubular acini that eventually converge to form 15-30 ducts. The acinar epithelium was a single or pseudostratified columnar epithelium. A single layer of cuboidal or flat epithelium may appear in some areas. The pseudostratified columnar epithelium is generally composed chiefly of principal and basal cells [38-40]. The chief cell shape of the human prostate is relatively regular. The nucleus is located at the base. In the chief cells, there are secretory vesicles at the top. Under the microscope, some secretory vesicles appeared hollow, while others contained dense condensates. The cytoplasm of the chief cells showed a well-developed Golgi apparatus. The principal cells were well differentiated and had intact organelles [41,42]. Basal cells are located between the principal cells and the basement membrane and have irregular morphology. The cytoplasm of basal cells was denser than that of principal cells. However, it contains fewer organelles and exhibits the characteristics of undifferentiated cells [43]. Principal and basal cells constitute the major cell types in different prostate zones [44]. In addition, recent studies have identified more specialized cell types. This further strengthens the understanding of the histological features of different prostate zones [45-47].

Different zones of the prostate have different histological features [14]. TZ had well-differentiated glands with epithelial cells of irregular size arranged in tall columns with clear cytoplasm [48]. TZ showed a high density of neuroendocrine cells [49]. Meanwhile, TZ had more collagen and muscle fibres than PZ [50]. TZ had denser mesenchyme and lower nerve density than PZ. In contrast, PZ showed regular-sized epithelial cells and sparse stroma. The acini of the PZ were relatively small and round, and the interstitium contained a loosely arranged network of smooth muscle fibres [26]. Meanwhile, it was observed that PZ had more neural branches than TZ [51]. Based

on the same study, increased neural branching in the PZ may be associated with carcinogenesis. The histological features of CZ were large and irregular acini. CZ had a larger nucleus, while the cell membrane was not apparent [8,13,50,51].

EMBRYONIC ORIGINS OF THE DIFFERENT ZONES OF THE PROSTATE

The embryonic development of the prostate was very complex. It was generally believed that the prostate arises from the primitive urogenital sinus. The primitive urogenital sinus is formed at about the fourth week of the embryo and begins to develop at about the seventh to eighth week of the embryonic period [52]. At the 10th week of the embryonic stage, the urogenital sinus grew outwards from the intrinsic epithelium around the urethra to form Prostatic buds: Testicular androgen-induced buds' elongation, branching, and epithelial differentiation. Every fifth epithelial cell bud formed a paired structure that protruded into the mesenchyme and gradually developed into prostatic acini and ducts [53]. The prostatic ducts extended rapidly, became longer, formed multiple branches, and became stable. At the 13th week of embryonic development, about 70 primary glands appeared with obvious cell differentiation potential and secretory activity. By approximately the 16th week of embryonic development, the prostate completes differentiation [54].

Even though we have discussed the above, the information on the embryonic development of the prostate still needs to be improved. There are few studies on the embryonic origin of the three different prostate zones. Here, we outline the embryonic development of the prostate into four major stages. In the first stage, the increase in testosterone secretion becomes the cue for the initiation of prostate development. In the second stage, the urogenital sinus epithelial bud into the surrounding mesenchyme, the prostatic gland tissue growth begins to initiate, and epithelial branches begin to appear. In the third stage, branching morphogenesis accompanied conduit growth and gradually formed a mature conduit network. This process results in distinct prostate partitions within a single lobular organ [55]. In the fourth stage, the different compartments of the prostate were further differentiated to form functional glandular epithelial tissue with different cell types. In addition, studies reported that the appearance of the three zones observed in the adult prostate had different spatial and temporal origins [7,8,14]. The five pairs of prostate buds, guided by androgen signalling, promoted epithelial branching and contributed to developing stromal compartments. The PZ and TZ are hypothesized to arise from the urogenital sinus. In contrast, the CZ was reported to branch from the Wolffian duct, connected to the seminal vesicles and ejaculatory ducts [9,13,56].

ANDROGEN RECEPTOR AND PROSTATE ZONES

Androgen plays an essential role in the physiological process and pathological changes of the prostate. The differentiation of primitive urogenital sinus depends on androgen secreted by the testis. The type of testosterone that prostate development depends on is DHT. Thus, DHT is essential for differentiating the primitive urogenital sinus into the prostate [57-60]. Androgen and Androgen Receptors (AR) play an essential role in the physiological and pathological processes of the prostate. Mitotic activity induced by androgen in the prostate is associated with increased DNA replication and proliferation. The mitogenic response of prostate cells to androgens depends entirely on AR expression [61,62]. For a long time, the physiological and pathological relationship between androgens and their receptors in the prostate has been a research hotspot.

Testosterone is the primary type of androgen released into the blood [62]. In the prostate tissue, the proportion of DHT is up to 80%, which is about ten times the level of testosterone. Compared with testosterone, DHT has a stronger affinity with Androgen Receptor (AR) and more potent biological effects [61]. Thus, DHT is the primary type of androgen that regulates prostate growth. However, the mechanism of DHT-mediated prostate growth has not been fully elucidated for a long time. Regarding the mechanism of androgen-induced growth regulation in prostate cells, the initial hypothesis was that DHT exerts its biological effects by binding to intracellular AR. This ligand-binding complex binds to the epithelial nucleus through specific Androgen-Responsive Elements (ARE) and enhances or represses transcription through the promoters of androgen-responsive genes [63-65].

Notably, AR is differentially expressed in the PZ and TZ of the prostate. Studies have shown spatial distribution differences in the expression level of AR in the prostate. The results of Feneley et al., showed a more significant AR enrichment in PZ compared to TZ. This suggested that PZ was more androgen-dependent under physiological and pathological conditions [66]. In addition, studies have compared the effects of sex hormones on prostate stromal cells derived from PZ and over TZ [67]. The results showed that AR mRNA expression was higher in PZ than in TZ, and cell growth factors were secreted more in PZ than in TZ. All the above studies suggest that PZ is more biologically active than TZ when induced by sex hormones. Therefore, the driving effect of androgens and AR on the variability in different prostate zones is an essential biological basis for the marked differences between PZ and TZ.

DISCUSSION

There are significant differences in the characteristics of pathogenesis, histological characteristics, embryonic origin, malignant potential, and androgen expression among different prostate zones. However, the underlying biological mechanisms responsible for these differences remain elusive. Therefore, we collectively refer to these differences as "apparent differences". We speculate that "apparent differences" between prostate zones determine the susceptibility to disease in different zones: that is, differences in the susceptibility of TZ and PZ pairs to carcinogenesis and hyperplasia. The inherent differences in the physiological stages of TZ compared with PZ of the prostate are essential factors in the prevalence of BPH. The inherent differences in the physiological phase of PZ compared to TZ are essential factors in the prevalence of PCa.

CONCLUSION

We propose that differences in biology between zones are potential drivers of differences in morbidity characteristics across prostate zones. Therefore, tracing the biological mechanism of prostate pathological changes from the perspective of prostate zoning differences may reveal the fundamental mechanism of the origin region of prostate lesions. However, at present, the concept of lesion location has yet to be introduced into the diagnosis and treatment guidelines of prostate diseases. The tumour invasion zone difference is closely related to the clinical outcome of PCa patients. Therefore, the zone of origin of cancer should be included in the risk assessment of PCa. Therefore, in future studies, the zone of lesion origin for different prostate diseases should be reported; this location information is incorporated into clinical diagnosis and treatment. The corresponding treatment plan was formulated according to different prostate regions' physiological and disease characteristics. We hope to eventually form a "zones diagnosis and treatment standard for prostate lesions". This will provide more accurate guidance for the prevention and treatment of prostate-related diseases.

AUTHOR CONTRIBUTIONS

Conceptualisation, manuscript writing: X.D.Y. and S.S.Y. Critical revision of the manuscript: R.J.L. and Y.S.Z. All authors have read and agreed to the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this paper as no new data were created or analysed in this study.

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