Review

Prostate cancer: genetics, epigenetics and the need for immunological biomarkers

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Abstract: Epidemiological data highlight prostate cancer as a significant global health issue, with high incidence and substantial impact on patients' quality of life. The prevalence of this disease is associated with various factors, including age, heredity, and race. Recent research in prostate cancer genetics has identified several genetic variants that may be associated with an increased risk of developing the disease. However, despite the significance of these findings, genetic markers for prostate cancer are not currently utilized in clinical practice as reliable indicators of the disease. In addition to genetics, epigenetic alterations also play a crucial role in prostate cancer development. Aberrant DNA methylation, changes in chromatin structure, and microRNA (miRNA) expression are major epigenetic events that influence oncogenesis. Existing markers for prostate cancer, such as prostate-specific antigen (PSA), have limitations in terms of sensitivity and specificity. The cost of testing, follow-up procedures, and treatment for false-positive results and overdiagnosis contributes to the overall healthcare expenditure. Improving the effectiveness of prostate cancer diagnosis and prognosis requires either narrowing the risk group by identifying new genetic factors or enhancing the sensitivity and specificity of existing markers. Immunological biomarkers (both circulating and intra-tumoral), including markers of immune response and immune dysfunction, represent a potentially useful area of research for enhancing the diagnosis and prognosis of prostate cancer. Our review emphasizes the need for developing novel immunological biomarkers to improve the diagnosis, prognosis, and management of prostate cancer. We highlight the most recent achievements in the identification of biomarkers provided by circulating monocytes and tumor-associated macrophages (TAMs). We highlight that monocytes-derived and TAMs-derived biomarkers can enable to establish the missing links between genetic predisposition, hormonal metabolism and immune responses in prostate cancer.

Keywords: cancer genetics; cancer epigenetic; tumor microenvironment; monocytes; TAMs; prostate cancer; cancer biomarkers

1. Epidemiology.

The World Health Organization (WHO) estimates that cancer was responsible for 10 million deaths in 2020, accounting for nearly one in six deaths. There were 1,414,259 new cases of prostate cancer (PCa) worldwide and 375,304 deaths from this type of cancer in 2020 according to the Global Cancer Observatory (GCO) (gco.iarc.fr). PCa ranks third in terms of incidence and second in terms of cancers affecting men globally [1]. In terms of mortality, PCa ranks eighth worldwide (Table 1). Overall, PCa statistics are relatively similar across different regions, although it ranks first among cancers affecting men in Latin America and eighth in Asia [2]. This suggests the potential impact of racial,

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ethnic, socioeconomic factors, and variations in the biology of prostate carcinogenesis, including the genetic predisposition of certain groups to develop biologically aggressive forms of the disease. Even when considering geographically diverse populations with similar access to healthcare, men of African descent have a higher incidence of PCa and worse prognosis. African American men, Caribbean men, and black men in Europe exhibit higher incidence rates than white men, with mortality rates approximately twice as high, indicating a genetic predisposition to PCa development [3, 4]. Analyses of PCa biopsies from men in sub-Saharan Africa have revealed a significant proportion of high-grade tumors (Gleason score 8+) However, variations in healthcare access and differences in cancer case registration across countries limit the reliability of conclusions regarding the correlation between race, ethnicity, geography, and PCa aggressiveness based solely on epidemiological data [3]. Furthermore, the significance of racial differences in PCa outcomes diminishes significantly if the male population in the analyzed countries has equal access to healthcare services [4–6].

Table 1. The epidemiology of prostate cancer in 2020 according to the Global Cancer Observatory (GCO) [2].

Region	Incidence			Deaths			5-year prevalence (all ages)	
	number	% of all sites	Rank	number	% of all sites	Rank	number	Per 100 000
World	1 414 259	7.3%	3	375 304	3,8%	8	4 956 901	126,13
Europe	473 344	10.8%	3	108 088	5.5%	5	1 873 814	518.11
Northern America	239 574	9.4%	3	37 192	5.3%	5	929 921	-
Latin America and the Caribbean	214 522	14.6%	1	57 415	8.0%	3	709 119	220.48
Asia	371 225	3.9%	8	120 593	2,1%	14	1 176 781	49.59
Africa	93 173	8,4%	3	47 249	6.6%	4	178 197	26.60
Oceania	22 421	8.8%	2	4 767	6,9	4	89 069	416.92
Russia Federation	46 454	7,9%	3	14 434	4,6	7	169 221	250.18

The worldwide incidence and mortality of PCa are strongly correlated with increasing age, with the average age at the time of primary diagnosis being 67 years [7]. Epidemiological studies conducted globally have reported the highest incidence of PCa in individuals aged 75-79 years. In 2022, the incidence rates were recorded as 155 cases per 100,000 for ages 55-59, 510 cases per 100,000 for ages 65-69, and 751 cases per 100,000 for ages 75-79 [2].

Nineteen international studies, spanning from 1935 to 2014 and including countries such as Scandinavia, Caucasus, France, Hungary, Greece, Japan, China, Singapore, and North America, examined the histopathological evidence of PCa in autopsies of 6,024 males aged between 50-59, regardless of the cause of death. These studies found that approximately half of the individuals had histopathological evidence of prostate cancer, although only 3.8% died from PCa [8].

The prognosis for patients newly diagnosed with PCa varies significantly depending on the stage of the disease. If the disease is detected at early stages, men with localized PCa can have a life expectancy of up to 99% for more than 10 years, depending on age, comorbidities, and chosen treatment strategy [9]. International statistics indicate that around 5% of men diagnosed with PCa develop distant metastases, and the overall five-year survival rate for metastatic disease is 30% [9]. Almost all patients with metastatic PCa eventually progress to a castration-resistant form that is resistant to

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androgen deprivation therapy. These factors contribute significantly to the morbidity and mortality associated with PCa [9].

While it is widely recognized that the immune system plays a crucial role in controlling cancer initiation and progression, there has been insufficient attention given to epidemiological studies examining the link between immune status, subclinical inflammation of infectious or endogenous origin, and the incidence of prostate cancer. It would be of great interest to further investigate how inflammation, leading to subclinical activation of innate immunity, may facilitate the development of prostate cancer.

2. Genetic predisposition for prostate cancer

2.1. Genetic markers of PCa

The vast majority of PCa cases are sporadic and caused by turning off tumor suppressor genes and turning on oncogenes and only up to 5-10% of PCa cases have family history, and are caused by germline mutations [10]. The presence of a first-degree PCa relatives is a risk factor associated with a two- to three-fold PCa compared to men without a family history of PCa [11]. Epidemiological and case-control studies have shown the inheritance of specific mutations in PCa susceptibility genes and reported that patients with these mutations have an increased risk of the disease [9]. Thus *BRCA 1/2* germline mutations in men increase the risk of PCa relative to the average population level by 3-8 times. Genetic alterations in *BRCA2* in PCa patients are associated with aggressive behavior of the disease [11]. Sequencing of DNA samples in men with a family PCa history reveals a high frequency of DNA repair gene mutations, such as *BRCA1/2*, *HOX*, *ATM*, *CHECK2*, *PALB2 and RAD51D*, *RNase L* (*HPC1*, lq22), *MSR1* (8p), and *ELAC2*/*HPC2* (17p11) (Figure 1) [12]. They are involved in the maintenance of genome stability, particularly in the processes of repair by homologous recombination (HRR), repair of misfolded nucleotides (mismatch repair - MMR), also inter-chain DNA cross-links. *BRCA1* and *BRCA2* genes predisposing to PCa are also found to be involved in pathways of control of checkpoints for DNA damage and replication fork protection during replication [13].

PCa tumor cells are characterized by genome instability both at chromosomal and gene levels. Genomic gains of chromosomes 7 and 8q and heterozygous losses of 8p, 13q, 16q , and 18 are often met in PCa [14]. Besides, PCa tumors contain a large number of structural gene rearrangements, primarily translocations and deletions, the number of which increases markedly with the disease progression. More than half of primary PCa patients (up to 70%) show formation of the chimeric oncogene *TMPRSS2-ERG* - a product of fusion of the 5'-untranslated region of androgen-regulated gene *TMPRSS2* (chr21q22.2) with ETS family of transcription factors genes, namely ERG (chr21q22.3) that results in aberrant expression of ERG [14–17]. *TMPRSS2:ERG* fusion is an early event in prostate carcinogenesis, it is absent in benign prostate hyperplasia (BPH) and in normal prostate tissues and is considered as diagnostic and prognostic marker for PCa [18–20]. ERG-positive PCs are associated with a distinct spectrum of hypermethylation accompanied by epigenetically silenced genes, revealing a greater molecular and biological diversity (Cancer Genome Atlas Research Network, 2015). Numerous studies have found a correlation between fusion of the *TMPRSS2* and ETS family genes (*ERG, ETV1, ETV4*, *ETV5*) and PCa [18]. The fusion of these genes makes it possible for the ETS genes to be activated under by the action of activators of the *TMPRSS2* gene, thus triggering the cancer process in prostate cells [17]. *ERG* fusion genes are regulated by androgen receptor. In primary PCa, *ERG* binds and involve transcription factors AR, FOXA1, and HOXB13 leading to activating the Wnt and Notch pathways [21], [22]. In *ERG*-positive PCa cases with PTEN loss PI3K signaling is shown to be activated that results in increased proliferation and invasion. There are no specific prognostic biomarkers for *ERG*-positive tumors [23]. But it's important to note that aggressive *ERG*-negative PCa is associated with *SPOP*/*FOXA1* mutation, *CHD1* (5q15-q21) deletion, and *SPINK1* expression. Gleason scale, PSA, and other biomarkers are exclusively for *ETS*-negative patients [24].

Primary PCa germinal and somatic tumors are very diverse genetically. In recent years, due to the rapid development of molecular genetic methods, new approaches to genetic testing were

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developed. Next Generation Sequencing (NGS) has been introduced into clinical practice and has opened a new approach to genetic testing. It allows to perform multiple genes panel testing of germline and somatic mutations, and to identify rare variants in genes with moderate penetrance [25]. The presence of these mutations leads to an increased risk of PCa phenotype over a lifetime by 35–60%. The Cancer Genome Atlas (TCGA) consortium reported recurrent mutations or copy-number alterations within the following genes - *SPOP, FOXA1, IDH1, TP53, PTEN, PIK3CA, BRAF, CTNNB1, HRAS, MED12, ATM, CDKN1B, RB1, NKX3-1, AKT1, ZMYM3, KMT2C, KMT2D, ZNF770, CHD1, BRCA2, CDK12* [14]. Recent investigations revealed metastatic castration-resistant PCa have a similar mutational landscape, but it harbored a higher mutational load and frequency of large-scale structural variants compared to primary PCa [14]. However, the list of driver genes remained almost similar *PRAD; AR, TP53, MYC, ZMYM3, PTEN, PTPRD, ZFP36L2, ADAM15, MARCOD2, BRIP1, APC, KMT2C, CCAR2, NKX3-1, C8orf58*, and *RYBP*, except AR gene mutations which were the result of PCa treatment [26]. Somatic alterations affecting AR expression, AR gene amplifications and treatment-associated mutations have been detected to be a major driver of castration resistance [26].

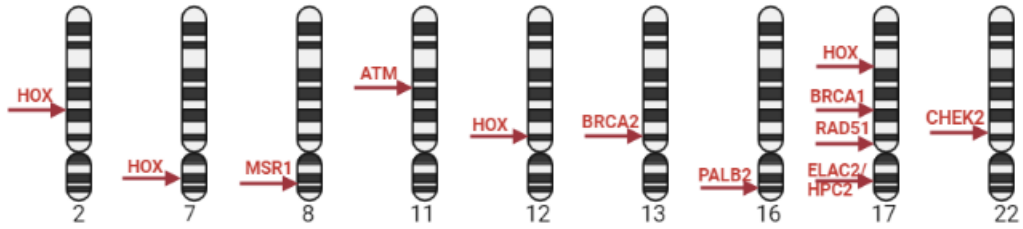

Figure 1. The location of mutations in DNA repair genes detected by sequencing DNA samples from men with a family history of prostate cancer.

2.2. GWAS in PCa

Genome-wide association studies (GWAS) with the use of multi-ancestry approach are necessary to discover new risk variants for prostate cancer, to refine lead variants in known risk regions and to develop genetic risk scores for PCa for effective stratifying PCa across populations. To date GWAS and precise mapping studies of PCa have been mainly performed in men from European, African, East Asian and Hispanic populations to identify common genetic variants associated with disease risk across populations [27]. Approximately 270 loci harboring hundreds of single nucleotide polymorphisms (SNPs) associated with PCa risk have been revealed [27]. PCa susceptibility loci were found on all chromosomes except chromosomes 15, 16, 21, and 23. PCa risk-associated SNPs were highly enriched in noncoding cis-regulatory genomic regions [28]. Of 191 independent and replicated associations that reached genome-wide significance (i.e., $p<10^{-8}$), 123 (64%) were reported in populations of European origin, 21 (11%) in populations of Southeast Asia and 45 (24%) in other populations. Only one locus (17q21) reached genome-wide significance in populations of African ancestry [28]. Khan et al. showed little heterogeneity in associated PCa variants across populations [3]. However, many loci found in populations of European or Asian ancestry were not replicated in populations of African ancestry, or the effect size was smaller (or directly opposite) for the race [3]. Several hypotheses have been proposed to explain the complexity of replication and differences in the magnitude of genetic effects depending on race and ethnicity. First, the underlying genetic predisposition, and hence the biology of PCa, can differ fundamentally by racial or ethnic group [29]. This explanation has limitations, as it implies that the biological basis of PCa depends on race or ethnicity. However, this hypothesis cannot be ruled out based on the available data. The most accurate explanation is that risk alleles and the underlying population structure of PCa susceptibility loci differ by

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ethnicity or race, and that these differences likely affect the ability to detect genetic associations [29]. Polymorphic variants in the 8q24 region are associated not only with PCa, but also with other cancers in different populations [29]. However, the biological mechanism of the influence of SNPs in this region, leading to prostate carcinogenesis, is unclear, since this region does not contain any coding DNA regions. The closest gene to this region is *MYC*, a proto-oncogene that is disrupted during carcinogenesis [29]. The 8q24 region may influence the expression of *MYC* gene. The influence of 8q24 on Wnt signaling has also been determined [29]. As a result of the OncoArray project, 63 new loci associated with PCa susceptibility have been identified, 52 of them were identified by imputation of OncoArray genotyping data [30]. A novel 6q27 variant (rs138004030) was found to be significantly associated with early PCa onset [30]. Among the new 63 variants, several candidate genes were revealed; one of them is a missense variant of *ATM* gene rs1800057 [31]. Although this missense mutation was classified as "benign" in the ClinVar database, *ATM* has been implicated in the development of PCa and is strongly associated with the aggressive course of the disease. The ATM protein is a key checkpoint kinase that acts as a regulator of a wide range of downstream proteins, including TP53 and BRCA1, the CHEK2 checkpoint kinase, the RAD17 and RAD9 checkpoint proteins, and the NBS1 DNA repair protein [31]. Another missense variant (rs2066827) has been identified in *CDKN1B* gene (cyclin-dependent kinase 1B inhibitor), which belongs to the Cip/Kip family of cyclin-dependent kinase inhibitors [29]. *CDKN1B* controls cell cycle progression to the G1 stage, and in vitro studies have shown that *CDKN1B* levels to be associated with increased tumor size and tumor grade [29]. This particular variant has previously been associated with familial PCa and disease progression. One more candidate gene *RASSF3* rs7968403 has been identified. *RASSF3* is a plasma membrane GTP-binding protein and it is a member of the RAS signaling pathway that is aberrant in about one-third of cancers [29]. GWAS meta-analysis for Japanese and Chinese populations identified rs12791447/11p15.4 and rs58262369/14q23.2. The rs58262369 polymorphic locus is located in the 3'-untranslated region of *ESR2*, which encodes for estrogen receptor 2 [32]. Animal studies have shown high expression of *ESR2* in normal prostate epithelial cells, and *ESR2* knockout mice develop prostatic hyperplasia [32]. TCGA data showed that *ESR2* is upregulated in prostate tumors compared to normal prostate tissues, however, this does not correlate with increased mRNA expression [32]. rs12791447 is located in the intron of the *PPFIBP2* gene. According to TCGA, the expression level of this gene is significantly lower in tumors compared to normal prostate tissue [32]. To date, almost all available GWAS data have been obtained for the population of Western Europe and the white population of North America (79.8%, [33], therefore, further research is needed with the inclusion of populations from other regions, which will supplement existing information and will identify risk factors specific to different populations [34]. A population-specific approach and the ability of homogeneous populations to detect disease-specific SNPs is important for GWAS studies. At the same time, homogeneous population material provides a resource for checking previous GWAS results performed on mixed populations.

Future GWAS results will provide further support for a contribution of germline variation to ancestry differences in PCa incidence. The clinical benefit of genetic risk scores profiling for targeted screening and early diagnosis also needs to be examined, and larger PCa consortia in men of non-European ancestry will be required to identify additional risk variants, to improve precision of risk estimation and to enhance the predictive ability of the genetic risk scores across populations [33].

Despite the numerous genetic studies of PCa, the results obtained during investigations are contradictory; they are poorly replicated in studies of different populations and are characterized by significant interethnic differences. The wide variability of clinical manifestations of PCa indicates the need to study both general genetic risk factors for the development of the disease and specific factors predisposing to certain clinical and pathogenetic variants of disease course. It has to be taken under consideration, that immune system has strong impact on the creation of permissive conditions both for the initial cell transformation, as well as for the support of primary tumor growth and metastatic spread. Therefore, genetical aspects have to be considered on the immunological landscape, that is affected by lifestyle, exposure to pathogens, and chronic low grade inflammation driven by metabolic and stress factors. In this regard, the identification of risk factors specific for the development of PCa

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in different populations is relevant. Identification of PCa risk markers will make it possible to predict the risk of PCa development with high accuracy and to develop preventive measures taking into account the individual genetic characteristic of each patient.

It is necessary to confirm previously identified markers, to exclude false positive findings is an essential step to evaluate GWAS findings. Thus, replication and validation studies are an effective approach that will enable to disprove random findings and possible random associations. Moreover, in order to bring the genetic aspects in the overall pathophysiological context, it is necessary to analyze how potential genetic predisposition affects PCa risks in the immunocompromised patients. However, such analysis is far away from being trivial, since number of factors can be associated with the compromised immune system. For example, studies on PCa in HIV-infected men are complicated by the significantly enhanced incidence of HIV infection in sexual minority groups while such important parameter as sexual orientation is not routinely included in cancer registers [35]. Additional factors is that sexual minorities can experience poorer health-related quality of life outcomes compared to heterosexual men [35].On another side, the incidence of PCa might be decreased in men from sexual minorities living with HIV due to their shorter life expectations.

2.3. GWAS and PCa aggressiveness

The majority of men diagnosed with PCa demonstrate indolent PCa; therefore, detecting the genetic variants that are able to distinguish aggressive PCa from non-aggressive one is of critical clinical importance for the prevention and treatment of the disease.

A few GWAS devoted to discovery of SNPs for prediction of aggressive PCa have been conducted world-wide [36–44]. Risk assessment of PCa is an important tool to distinguish between low-risk from high-risk PCa, preventing PCa overtreatment and helps to choose the optimal and provide tailored treatment strategies for each patient. In 2007, Duggan et al. were the first to conduct a GWAS study for aggressive PCa [36]. They performed genome-wide association scan in 498 men with aggressive PCa and 494 control subjects from Sweden. Among 60,000 SNPs they identified seven that had a similar (positive or negative) and statistically significant (P<.01) association with the risk of aggressive PCa in both studies. Analyzing 1032 PCa patients and 571 control subjects of European descent showed that only rs1571801 has maintained a significant association after the validation stage and was associated with aggressive PCa (one-sided P value = 0.004). (OR: 1.36; 95% CI: 1.13–1.63; p = 1.0 × 10-3). It is located in the *DAB2IP* gene, which encodes a novel Ras GTPase-activating protein and putative prostate tumor suppressor. Interestingly, the association of this SNP was stronger in patients with a Gleason score higher than 8 [36].

Jielin Sun et al., 2009 found the association of rs9623117*C allele at 22q13 with aggressiveness of PCa. The combined allelic test was highly significant, with P = 5.0 x 10(-7). The odds ratio (OR) of allele C for aggressive PCa was estimated to be 1.18 [95% confidence interval (95% CI), 1.11-1.26]. The risk-associated variant was located within the genomic region of *TNRC6B*, a gene involved in miRNA-mediated mRNA degradation [37].

One of the studies enrolled 4,829 and 12,205 patients with more and less aggressive disease but did not collected control individuals without prostate cancer. They found that the frequency of the TT genotype of SNP rs4054823 at 17p12 was consistently higher among patients with more aggressive compared with less aggressive disease in each of the seven populations studied, (P= 2.1 x 10(-8)) under a recessive model, exceeding the conservative genome-wide significance level. The difference in frequency was largest between patients with high-grade, non-organ-confined disease compared with those with low-grade, organ-confined disease. This study demonstrates that inherited variants predisposing to aggressive but not indolent PCa exist in the genome, and suggests that the clinical potential of such variants as potential early markers for risk of aggressive PCa should be evaluated. The rs4054823 variant is located in an intergenic region, with the closest gene being *HS3ST3A1*, which encodes a heparan sulfate biosynthetic enzyme, a protein with no known relation to PCa [38]

The investigation of Liesel M FitzGerald et al., 2011 has analyzed 387,384 autosomal single nucleotide polymorphisms (SNPs), and rs6497287 located on 15q13 chromosome was confirmed to be

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most strongly associated with more aggressive (P(discovery) = 5.20 × 10(-5), P(validation) = 0.004) than less aggressive disease (P = 0.14) [39]. Besides, rs3774315 on 3q26 was found to be associated with PCa risk; however, the association was not stronger for disease that is more aggressive. Study cohorts included 202 PCa cases with aggressive phenotype and 100 randomly sampled, age-matched prostate-specific antigen screened negative controls. Validation testing in an independent set of 527 cases with more aggressive and 595 cases with less aggressive prostate cancer, and 1,167 age-matched controls confirmed the results obtained [39]. Another study enrolled patients with aggressive forms of PCa and biopsy-proven normal controls ascertained from a PCa screening program to GWAS [40]. They found significant associations between aggressive PCa and five single nucleotide polymorphisms (SNPs) in the 10q26 (rs10788165, rs10749408, and rs10788165, p value for association 1.3×10^{-10} to 3.2×10^{-11} and 15q21 (rs4775302 and rs1994198, p values for association 3.1×10^{-8} to 8.2×10^{-9} regions. Replication study proved the association of combinations of these SNPs in 3439 patients undergoing a prostate biopsy, to be associated with aggressive forms of PCa [40].

One of the most powerful investigations was performed by Amin Al Olama et al [42]. They conducted bioinformatical analysis of previously published GWAS and enrolled datasets of 11085 cases, where c patients had an aggressive disease form and 11463 were healthy individuals. The analysis of 2.6 million SNPs revealed rs11672691 to be significantly associated with aggressive PCa (OR=1.12; 95% CI=1.03–1.21). Validation studies comparing aggressive and indolent PCa cases did not confirm the significance of association of rs11672691 with aggressive PCa risk [45]. The risk allele of rs11672691 (intergenic) was associated with an increased risk for PCa-specific mortality and showed rs11672691 to be associated with both fatal and nonfatal PCa [45]. This intergenic variant is located on 19q13 chromosomal region within a long noncoding RNA gene - *PCAT19.* According to several investigations this SNP may be also involved in the regulation of *HOXA2*, *PCAT19* and *CEACAM21* expression, in PCa cell growth, invasion, metastasis and disease progression [46, 47].

Ping Gao J. et al described a statistically significant association of rs11672691 with clinical features of aggressive PCa, such as high tumor stage, high prostate-specific antigen (PSA) levels in 2738 men with disease progression and development of castration-resistant PCa (CRPC) [47]. They analyzed the expression of two previously unknown PCa genes, *PCAT19* and *CEACAM21*, and found that aggressive CRPC is associated with the G allele rs11672691, involved in regulation of *PCAT19* and *CEACAM21* gene expression and affects the cellular properties of the prostate tumor. It was hypothesized that analysis of the rs11672691 genotypes combined with analysis of *PCAT19* and *CEACAM21* gene expression levels may predict PCa recurrence and patient survival that may be useful in determining further follow-up tactics [42, 43, 48, 49].

The International Consortium for PCa Genetics (ICPCG) performed GWAS of 2511 (unrelated) familial PCa cases and 1382 unaffected controls, including 1394 PCa aggressive cases and 1096 less-aggressive ones, but none of the SNPs (rs2735839, rs11672691, rs11704416, rs35148638 rs78943174) previously associated with aggressive disease were significant in this investigation [42, 43, 48, 49].

Overall, all germinal mutations which have been highlighted by the studies in different geographical cohorts are found in genes related to the biology of cancers cells themselves, providing transformed cells with the enhanced potential to proliferate or migrate. However, such studies did not focus on the bioinformatics search in the screening data for the mutations in genes that make immune system more permissive for the transformed cells to start uncontrolled proliferation and invasion.

3. MiRNA as prostate cancer biomarker

Despite the significant advances in early diagnosis and treatment, the identification of new markers and design of diagnostic panels of molecular markers providing high accuracy and specificity in discrimination between aggressive forms of PCa and indolent forms, and predicting tumor aggressiveness, is still a relevant challenge. New biomarkers with high precision and specificity are needed for early detection of malignant changes and for population screening to identify predisposition to the development of PC, for disease prognosis and for making therapeutic decisions [49].

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Currently the main problem with the diagnostic management of PCa is the poor accuracy of currently available tools. Prostate biopsy performed when the serum prostate-specific antigen (PSA) level is above 2.5-4 ng/mL and/or abnormalities are detected during digital rectal examination confirms the diagnosis of PCa in 24-37% of cases [50].

The discovery of a new class of noncoding RNAs- microRNAs (miRNAs) is a promising new direction in the early diagnosis of PCa [52, 53]. Each miRNA can modulate the expression of multiple mRNAs and, furthermore, each mRNA may be targeted by several different miRNAs. Most of the physiological processes are controlled by miRNAs. MiRNAs are involved in the regulation of such cellular functions as the maintenance of stemness, proliferation, differentiation, apoptosis, and metabolism [53, 54]. About 60% of all human genes are regulated by miRNAs [55-57]. Aberrant expression of miRNAs may have a significant influence on some specific features of cell biology, ultimately leading to various pathological phenomena, including cancer [52]. Epigenetic regulatory mechanisms play a key role in cancer development and epigenetic events are one of the earliest in carcinogenesis [36, 37].

MicroRNAs (miRNA) are short noncoding single-stranded RNA molecules, that regulate post-transcriptional gene expression by complementary binding to the 30 untranslated region (3′-UTR) of mRNAs, which, in turn, lead to translational suppression or degradation of the mRNA target. MiRNAs play a crucial role in regulating several biological processes needed to preserving homeostasis and immune balance as they carry out a wide modulatory activity on various molecular signaling pathways. Evidence for their crucial role in prostate carcinogenesis and progression, their stability in biological fluids make microRNAs promising candidates as non-invasive or minimally invasive diagnostic and prognostic biomarkers of PCa.

3.1. MicroRNA biogenesis

In mammals, more than 90% of microRNAs are encoded by nucleotide sequences located in introns. For comparison, this value constitutes 14% in fruit flies and invertebrates [57]. MiRNA biogenesis consists of several stages. At the initial stage, miRNA genes are transcribed by RNA polymerase II, resulting in the formation of precursor miRNAs (pre-miR) that contain from several hundred to several thousand nucleotides. The next stage is catalyzed by ribonuclease III (Drosha) and the RNA-binding protein Pasha (DGCR8), resulting in the cleavage of the miRNA precursor and the formation of the primary miR (pre-miR), which usually consists of about 70 nucleotides [58]. The nuclear transporter factor, exportin-5, subsequently binds to the pre-miR and translocates it into the cytoplasm, where another RNAse, Dicer, interacts with the pre-miR, resulting in the formation of mature RNA duplex consisting of about 22 nucleotides [59]. Mature miRNA in the complex with the Argonaut (Ago2) and TRBP family proteins forms RISC (RNA-induced silencing complex). One of the miRNA duplex strands (passenger strand) is degraded, and the functional strand activates RISC complex and interacts with target mRNA, resulting in the degradation of this target mRNA and inhibiting its translation [60]. Imperfect binding leads to poor contact between the microRNA and target mRNA with subsequent inhibition of translation, while a high degree of complementarity promotes strong binding and proteolytic cleavage of target mRNA with the involvement RISC complex. In the past several years, non-canonical biogenesis pathways of miRNAs such as the synthesis pathway continue to be discovered, but most pathways still require Dicer enzymes [61]. The mirtron pathway is the first non-classical pathway discovered. This pathway does not require the Drosha/Dgcr8 complex to generate pre-miRNA, but still requires the transport of XPO-5 and the cleavage of Dicer enzyme [62].

3.2. The role of miRNA in prostate carcinogenesis

The profiles and functions of miRNAs are altered in different cancer types and their nature varies [54]. miRNA can exert a negative effect by altering the expression level by either loss or increase in the affinity of miRNA sequences within or on its target. The miRNA function is largely determined by the relative accessibility of the target mRNA. For these reasons, individual miRNAs may have different effects in tissues, especially in cancers of different cellular origin [57, 64].

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Porkka et al. conducted the first study on the expression profiles of 319 miRNAs in PCa with oligonucleotide array hybridization and found differential expression of 51 miRNAs between benign tumors and carcinoma tumors was detected, 37 of them showing down-regulation and 14 up-regulation in carcinoma samples [64]. However, not all of the results of Porkka et al. were confirmed by further research. At present, the number of platforms developed for the study of the miRNA expression profiles is rapidly increasing. For the analysis of tumor-specific microRNAs, microarrays are often used. However, this method was based on previously accumulated data on miRNAs. Bioinformatic analysis of the data identifies a pool of miRNAs that influence PCa carcinogenesis (Figure 2) [65]. However, experimental data have confirmed that not all of the mentioned miRNAs impact the development of malignant prostate tumors. The next-generation sequencing (NGS) technology provided a new approach to identify previously unknown miRNAs. The most appropriate method to confirm the miRNA expression profile is real-time quantitative PCR (RT-qPCR)[66].

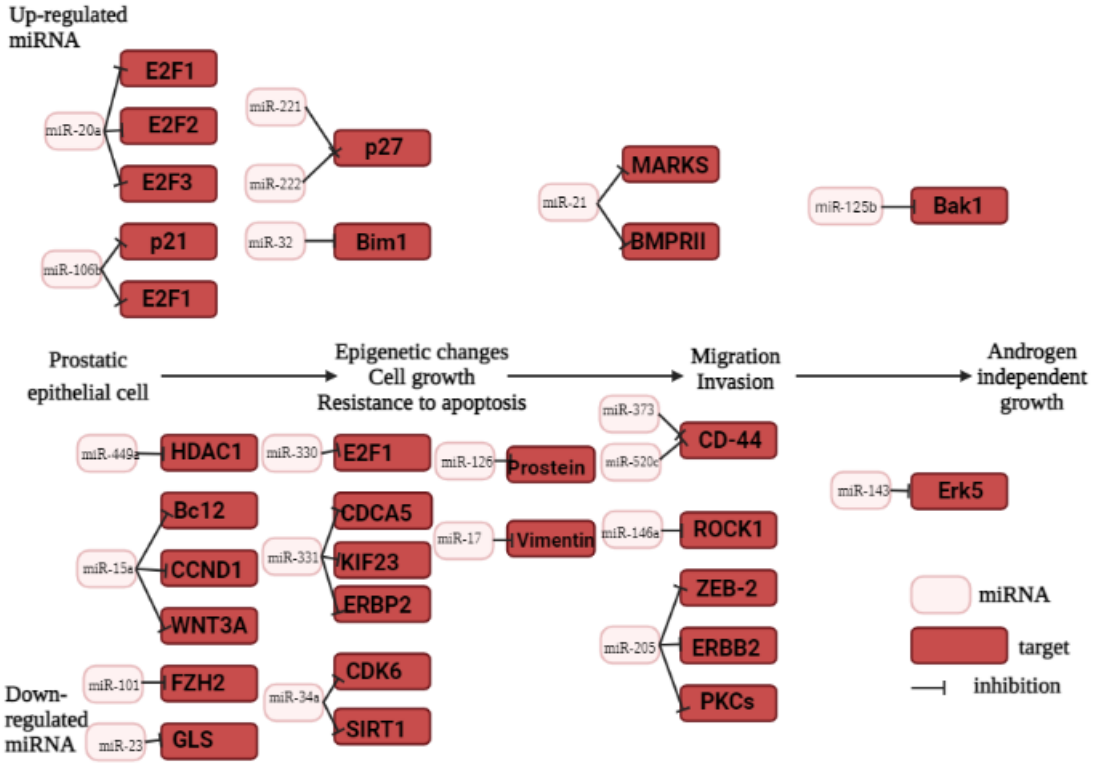

Figure 2. The up-regulated and down-regulated miRNA, and their role in the pathogenesis of prostate cancer.

3.3. Oncogenic miRNAs in prostate cancer

In malignant tumors of various origin, the expression of majority of miRNAs is reduced. This is consistent with the existing view on the association between miRNA expression and differentiation. However, microRNAs with amplified genes may have the functions of oncogenes. A number of these miRNAs were identified, as well as the well-known fact regarding the overexpression of oncogenic miR-181b in prostate cancer. Hu et al. demonstrated that the inhibition of miR-181b induced apoptosis in the PCa cells [67]. Katia et al. suggested that miR-21 negatively regulated RECK, a matrix metalloproteinase regulator, thereby providing the expression of the invasive properties of PCa cells [68]. In addition, miR-21 can promote the development of the aggressive potential of PCa cells through the regulation of other tumor inhibitors, such as MARCKS protein (Myris- toylated alanine-rich protein kinase c substrate), which is the target of miR-21 [69]. There are other tumor suppressor genes negatively regulated by miR-21, including *ANP32A* and *SMARCA4* genes [70]. Since miR-21 is overexpressed in prostate cancer, targeted inhibition of miR-21 restores apoptosis in the cells [69]. It

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should be also mentioned that the transfection of miR-21 into PCa cells induces resistance to the antitumor drug docetaxel [71]. Altered expression of miRNA-21 was demonstrated in numerous studies. Recent meta-analysis to assess reliability of miRNA-21 as diagnostic biomarker especially in progressivity of PCa showed miRNA-21 as reliable serum diagnostic biomarker candidate for metastatic progressive PCa. The pooled sensitivity and specificity showed 0.91 (95% CI 0.88-0.94, I2=0%) and 0.89 (95% CI 0.85-0.92, I2=44.8%), respectively. Positive and negative likelihood ratio showed 7.18 (95% CI 4.31-11.96, I2=56%) and 0.11 (95% CI 0.07-0.16, I2=11.8%). SROC were assessed and got Area Under Curve around 97.4% [72]. The expression values of miRNA-21 also correlate with the occurrence of resistant castration of PCa and metastases, therefore miRNA-21 is expected to be a biomarker to estimate the progression of cancer. Seputra et al 2021 examined forty-eight total samples obtained from serum and then performed RT-PCR to obtain expression values of miRNA-21 [72]. The cut-off value of miRNA-21 from the PCa category was 33.595-35.21, PPV = 87.5%, NPV = 66.7% with p value = 0.003, while the value of miRNA-21 in the castrate resistant PCa (CRPC) category was> 35.21, PPV = 80%, NPV = 58.3 with a value of p = 0.04. Taking into account the significant differences in the expression values of miRNA-21 between benign prostatic hypertrophy with CRPC and PCa and CRPC, miRNA-21 cut-off point is potential to differentiate the diagnosis [72].

Several studies identified miR-18a-5p as a tumor promoter in prostate cancer. The results of Liang et al 2021 suggest that miR-18a-5p might function as a tumor-promoting factor in PCa and might contribute to its proliferation [73]. They found miR-18a-5p expression to be upregulated in human PCa tissues while SLC40A1 was down-regulated. Cell proliferation assay demonstrated that miR-18a-5p promoted PCa cell proliferation. They also found out that SLC40A1 was downregulated by miR-18a-5p in PCa cell lines and restoration of SLC40A1 reversed the effects of miR-18a-5p in PCa cells [74]. Besides, diagnostic significance of miR-18a was shown among Egyptian patients. MiR-18a was a powerful discriminator of PCa patients from healthy controls as it had the highest AUC (0.966; 95% CI, 0.937-1.000), while miR-221 provided better differentiation of metastatic from localized PC (sensitivity was 92.9% at 100% specificity), and when miR-18a and miR-221were combined for differentiating patients with PC, that would increase the sensitivity to 96.4% at a specificity of 100% (AUC, 0.997; 95% CI, 0.988-1.0) ($p < .000$) [74].

It is known that the miR-106b-25 cluster is located in intron 13 of the *MCM7* gene (Minichromosome maintenance protein 7) [75]. The co-expression of *MCM7* and miR-106b-25 mediates prostatic intraepithelial neoplasia in transgenic mice) [75]. Moreover, PTEN expression is negatively regulated by miR-106b-25 [75]. It is interesting that miR-106b-25 regulates the *ZBTB4* (zinc finger and BTB domain-containing 4) at the post-transcriptional level. *ZBTB4* functions as a tumor suppressor gene and is involved in the inhibition of specific target gene expression by competitive binding with the promoter regions [75]. The miR-106b-25 cluster also negatively regulates caspase-7 [76]. There are conflicting data on the regulation miR-125b via androgen signaling. It is suggested that androgen receptor (AR) inhibits miR-125b to initiate the expression of various mRNA transcripts [77]. In contrast to these data, it was reported in one of the studies that androgen signaling stimulated miR-125b expression, while targeted inhibition of miR-125b led to a decrease in androgen-independent growth [78]. Moreover, miR-125b negatively regulates various proapoptotic genes, including p53, Puma, and Bak1 [79]. It was also demonstrated that microRNA-4534 (miR-4534) is overexpressed in PCa. MiR-4534 was found to be hypermethylated in normal tissues and cell lines compared to PCa tissues/cells. MiR-4534 exerts its oncogenic effects partly by downregulating the tumor suppressor PTEN gene. Knockdown of miR-4534 impaired cell proliferation, migration/invasion and induced G0/G1 cell cycle arrest and apoptosis in PCa. Hannah Nip et al., 2016 revealed that overexpression of miR-4534 induced procancerous characteristics in this non-cancer cell line. Statistical analyses revealed that miR-4534 has potential to independently distinguish malignant from normal tissues and positively correlated with poor overall and PSA recurrence free survival [80]. Information on oncogenic miRNA is summarized in Table 2.

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Table 2. Oncogenic miRNA in prostate cancer.

miRNA	Function	Experimental models (Cell lines, animal models)	Patient cohort, size, age, and geographic location, groups of comparison	Reference
miR-18a	Increasing cancer progression	-	160 patients, average age 56.8 ± 12 including stage I, II, and IV presented the National Cancer Institute Cairo compared to 50 normal control healthy male individuals	[74]
miR-21	Accelerating tumor invasion and inducing castration resistance	-	170 patient older 45 years from Zagazig University Hospitals, Egypt compared to 70 healthy men	[81]
miR-32	Inhibition of apoptosis and increased proliferation	transgenic mir-32 mice	-	[30]
miR-106/miR-25	Increasing cancer progression	LNCaP cells PC-3 cells	 -	[31]
miR-125b	Increase in cell proliferation and suppression of apoptosis	The human PCa cell lines: C4-2 CWR22Rv1 BCa cell lines: T24, TCC-SUP, UMUC3, TCC-5637, and 293T	-	[82]

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miR-141	Development of castration resistance	LNCaP cells PC-3 cells	-	[82]–[84]
miR-221/miR-222	Increased cell proliferation, invasion, cell survival	LNCaP, PC3	-	[85]
miR-375	Diagnostics	LNCaP, PC3	-	[84]
miR-650	Reduced expression of the cellular stress response gene 1 (CSR1).	PC3	216 patients from 45 through 79 years from Pittsburgh, USA compared with 77 healthy men	[86]
miR-4534	Downregulating the tumor suppressor *PTEN* gene	LNCaP, PC3		[80]

LNCaP cells are androgen-sensitive human prostate adenocarcinoma cells derived from the left supraclavicular lymph node metastasis from a 50-year-old caucasian male in 1977.

PC-3 is a cell line initiated from a bone metastasis of a grade IV prostatic adenocarcinoma from a 62-year-old male.

C4-2 is a cell line with epithelial-like morphology that was isolated from a human prostate cancer LNCaP cell subcutaneous xenograft tumor of castrated mouse

CWR22Rv1 human prostate carcinoma epithelial cell line derived from a xenograft

BC- bladder cancer

T24 a cell line established from a human urinary bladder cancer patien

TCC-SUP is a cell line isolated from the urinary bladder of a female with grade IV transitional cell carcinoma

UMUC3 is an epithelial-like cell that was isolated from the urinary bladder male of a patient and can be used in cancer research

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TCC-5637 is a cell line exhibiting epithelial morphology that was isolated from the urinary bladder of a 68-year-old, White male patient with grade II carcinoma

293T is an immortalized cell line derived from the embryonic human kidney that is transfected with sheared human adenovirus type 5DNA

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3.4. Tumor suppressor miRNAs in prostate cancer

MiR-15a and miR-16 function as a tumor suppressor by participating in the regulation of the expression of such oncogenes as *BCL2, MCL1, CCND1*, and *WNT3A* [75, 76]. It was reported that the injection of a new class of miRNA inhibitors, named antagomirs, in normal mouse prostate with the purpose of miR-15a and miR-16 silencing resulted in considerable hyperplasia [77-79]and an increase in survival, proliferation, invasion, as well as increased cancer disease severity in the immunodeficient NOD-SCID mice [80]. There is evidence suggesting low expression levels of these microRNAs in various malignancies, including chronic lymphocytic leukemia, pituitary adenoma, and prostate carcinoma. In humans, miR-15a and miR-16 are located in the 13q14.3 region of chromosome 13, which has been reported in the studies to undergo deletions not only in PCa but also in other cancers such as chronic lymphocytic leukemia, pituitary adenoma, mantle cell lymphoma, and prostate cancer. [81]. Zidan et al. showed that the expression of miR-15a and miR-16-1 was considerably decreased in 80% of the examined PCa samples as compared to normal tissues [81].

It is also known that expression of miR-224, miR-16, miR-31, miR-125b, miR-143, miR-145, miR-149, miR-181b, miR-184, miR-205, miR-221, and miR-222 is decreased in PCa [82]. miR-143 and miR-145 play an important role in the biology of PCa and act as tumor suppressors by inhibiting cell growth and activation of apoptosis [83]. MiR-205 is a tumor suppressor, the transfection of miR-205 in PCa cells induces apoptosis. Note that miR-205 is directly involved in stimulating the expression of the IL24 and IL32 tumor suppressor genes [87][84]. This miRNA also participates in down- regulation of Bcl-2. Enhanced apoptosis was observed in PCa cells with restored miR-205 (by means of treatment with cisplatin and doxorubicin) [84]. MiR-574-3p controls Bcl-xL and substantially induces apoptosis in the PCa cells. The expression of miR-574-3p in PCa is decreased[85]

The Polycomb group gene Bmi-1 is overexpressed in PCa stem cells; however, as was demonstrated previously, there was a decrease in Bmi-1 expression in cells treated with NVP-LDE-225 (erismodegib) [86]. The inhibitory effect of erismodegib on Bmi-1 expression is realized through up-regulation of miR-128. The introduction of antagomirs in the cells to knock down miR-128 revealed that erismodegib-induced apoptosis was significantly disrupted [86].

The potential applications of exosomal miRNAs in the treatment and diagnosis of PCa have gained increasing interest. Many studies highlight the potential for EVs to be collected from the blood as marker-containing capsules for both the diagnosis of PC and for making a determination of the patient's stage and prognosis. Thus, exosomal miRNAs miR-107 and miR-574-3p, were successfully quantified in the urine of men with prostate cancer. Recently, miR-375 and miR-141 were identified as the best markers for high risk PCa [88]. In addition, it was found that miR-141, miR-298, miR-346, and miR-375 were upregulated in serum from prostate patients compared with controls [89], [90]. The role of the miR-141 in PCa is further supported by a study that found that it could be a valuable diagnostic tool for patients with this disease [91]. Moreover, exosomal miR-141 could differentiate patients with localized PCa from those with metastatic PCa with higher AUC (0.869) in comparison with AUC of the PSA (0.775). Also, high diagnostic capabilities had the miR-196a-5p and the miR-501-3p with the AUC 0.73 and 0.69, respectively [92]. Perspective non-invasive biomarkers was found by Li et al. in urine samples collected from PCa patients, namely they shown remarkable upregulation of exosomal miR-451a and exosomal miR-486-3p/5p as compared to the healthy controls [93]. In addition, as a predictive biomarker for early detection and castration-resistance PCa was serve exosomal miR-423-3p [94]. It was also demonstrated, that the miR-125a-5p/miR-141-5p ratio was significantly higher in PCa patients compared to HCs. According to the data presented, the miR-125a-5p/miR-141-5p ratio appeared to perform better as an early PCa biomarker than either of the miRNAs taken individually [95]. Fredsoe et al. identiffied different miRs by qPCR in cell-free urine samples from patients with benign prostatic hyperplasia and from those with clinically localized PCa. Furthermore, they developed a new diagnostic model of three miRs (miR-222-3p*miR-24-3p/miR-30c-5p) which distinguished benign prostatic hyperplasia from PCa [78].

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Yao et al. found that hsa-miR-182 was the single most upregulated miRNA in PC tissue . Hirata etal. provided evidence that hsa-miR-182 promotes PC by targeting RECK, FOXF2, and MTSS1—tumor suppressor transcripts [96]. Also, it was shown that miR-146a is upregulated in PC cell lines and tissues, oncoMir potential was demonstrated [97]. MiR-15b-5p and miR-106b-5p were confirmed to be significantly upregulated in tissue of aggressive PCa when their level was associated with disease aggressiveness [98]. Furthermore, prognostic score combining the level of miR-15b-5p and miR-106b-5p with serum PSA level discriminated indolent PCa from an aggressive form with even higher analytical parameters [98]. Also, as a result of the comparison of tissue and peripheral blood mononuclear cells samples, it was idenntified that down regulated hsa-miR-494-3p, hsa-miR-3128, hsa-miR-8084 were common miRNAs [96]. Three (HIF1A, NHS,INSL4) targets identified for hsa-miR-494-3p, two (HIF1A, AVRP1A) for hsa-miR-3128 and three (AVRP1A, NHS, INSL4) for hsa-miR-8084. These results suggested that hsa-miR-494-3p, hsa-miR-3128, hsa-miR-8084 and their targets may play a crucial role in therapeutic and early diagnostic strategies for PCa [96].

4. Pathogenesis and staging

PCa is the result of a complicated synergistic action of accumulated genetic changes aimed at boosting cell proliferation compared to cell death. Detection and recognition of these events is essential for disease control in the earliest stages of transformation, for developmental progression to an invasive tumor, for prognosis and determining points of therapeutic intervention. There is epidemiological evidence that indicates a potential association between symptomatic prostatitis and the risk of developing prostate cancer. [100–102]. Data from 746,176 patients over 50 years of age diagnosed with PCa from 2010 to 2013 were analysed, with follow-up to 2019 using the Korean National Health Insurance Service patient database [102]. Control groups were matched for age, disease (diabetes, hypertension), and Charlson comorbidity index. The incidence of PCa was statistically significantly higher in the prostatitis group (1.8% vs. 0.6%, $p<0.001$). The HR for patients with PCa was significantly higher in patients with prostatitis (HR 2.99; 95% CI 2.89-3.09, $p<0.001$), with HR for PCa being significantly higher in acute prostatitis than in chronic prostatitis (3.82; 95% CI 3.58-4.08; $p<0.001$; HR 2.77; 95% CI 2.67-2.87, $p<0.001$)[102].

The exact mechanisms underlying the association between prostatitis and PCa risk are not fully understood. However, several factors have been proposed, where inflammation plays a prominent role. Prostatitis is characterized by inflammation of the prostate gland. Chronic inflammation can lead to DNA damage, and alterations in cell signaling pathways [103]. Inflammatory processes in the prostate can result in the release of various cytokines and growth factors. These molecules can promote cell proliferation, angiogenesis (formation of new blood vessels), and tissue remodeling, which are all processes involved in tumor development and progression [104]. The immune response triggered by prostatitis may involve the recruitment of immune cells, such as macrophages and T-cells, into the prostate gland. Although these immune cells are intended to fight infection, their prolonged presence may contribute to chronic inflammation and create conditions favorable for evading immune surveillance [104]. It is important to note that while the association between prostatitis and PCa risk has been observed in epidemiological studies, not all individuals with prostatitis will develop prostate cancer. Further research is needed to better understand the complex mechanisms underlying these correlations and to identify potential therapeutic targets for intervention.

As mentioned above, uncontrolled activation of signaling pathways (which can be caused by inflammation), activated growth factors, in particular signaling through the lipid kinase group phosphoinositide 3-kinase (PI3K), contributes to carcinogenesis. [105]. As part of the activation mechanism, the catalytic subunits of PI3K, directly bind to small GTPases, which appear to be members of the RAS subgroup. The role of PTEN in this pathway is to catalyze the opposite reaction by metabolizing PI3K [105]. Eventually the triggering of signaling pathways leads to genomic instability, increased cell proliferation, cell invasion and migration (Figure 3).

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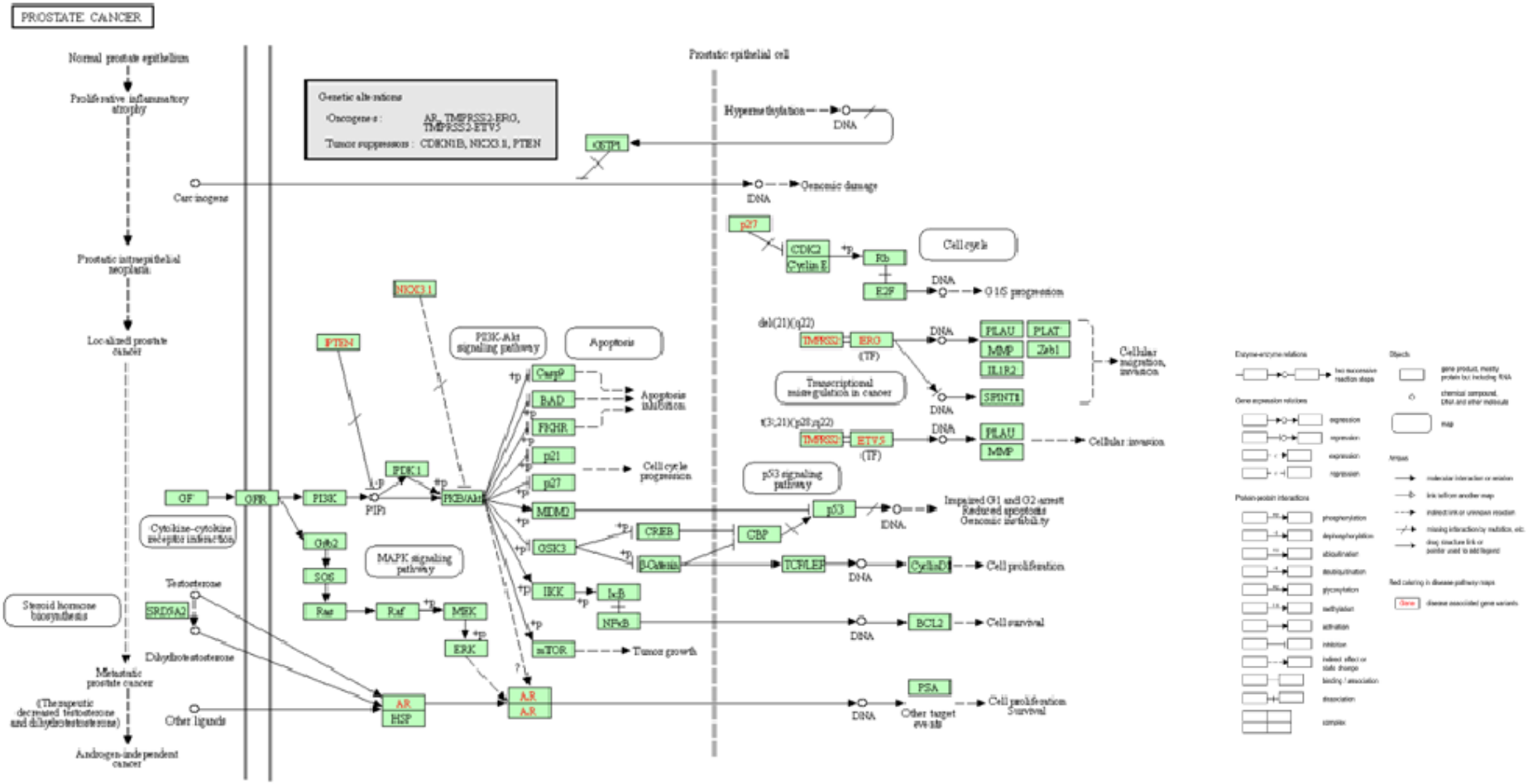

Figure 3. Prostate cancer pathways [65]. This is a schematic presentation of prostate cancer pathogenesis, driving factors, and connections between genes, signalig pathways. Key events in carcionogenesi include DNA hypermethylation, triggering the MARK signaling pathway, which leads to cell proliferation and tumor growth. Open question are marked in red.

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In the majority of patients localized PCa is multifocal, due to the fact that cancer most often occurs in the peripheral zone of the prostate, the surrounding pseudocapsule is involved in 80% of clinically detected cases of cancer [107, 108]. In the following stages, the cancer cells invade the seminal vesicles, paraprostatic tissue, which is regarded by the international TNM classification as T3 or in the urinary bladder, levator muscles, external sphincter and/or anterior abdominal wall - T4 stage [108]. The T1 stage of PCa is typically assigned when the tumor is confined to the prostate gland and is clinically non-palpable and non-visualized. This means that the tumor was detected either during a prostate biopsy performed due to elevated PSA levels or incidentally during a transurethral resection. In other cases where the tumor does not extend beyond the prostate, it is classified as stage T2 [108]. Lymphatic metastasis involves the hypogastric, obturator, external iliac, presacral, common iliac, or retroperitoneal lymph nodes. Depending on the spread of the tumor to regional or distant lymph nodes, the diagnosis is N1 or N2, respectively. When PCa spreads through the hematogenous route, it most often involves the bones of the axial skeleton, and less often the lungs, liver, and other soft tissues, which is assessed as stage M1 [109, 110].

Risk assessment of PCa at diagnosis and after treatment is based on the grading system, PSA level, tumor-node-metastasis classification (TNM), and/or previous treatment history in order to predict potential fatal outcomes of PCa and justify treatment decisions. Some patients with intermediate-risk PCa and every high-risk PCa patient should undergo additional imaging studies [87–89].

Signs of chronic inflammation are a common finding in malignant prostate tissues. By histological examination, inflammatory infiltrates are defined mainly by CD3+ T lymphocytes, CD19 or CD20 B lymphocytes (10-15%) and macrophages (15%) [110]. It is likely that the damage associated with the inflammatory response and subsequent chronic tissue healing can lead to proliferative inflammatory atrophy (PIA).

Currently, there exists inadequate evidence to definitively establish a direct causal connection between prostate inflammation and prostate cancer. Ongoing investigations aim to explore a potential association between these two conditions; however, additional dependable and precise evidence is necessary to firmly establish this association. For instance, it has been suggested that the absence of glutathione S-transferase P1 (GSTP1) might be accountable for the progression from prostatic inflammation to high-grade intraepithelial neoplasia (HGPIN) and prostate cancer (PCa) in individuals with a genetic predisposition [110]. Conducting further research will enable us to gain a better understanding of these mechanisms and their impact on the development of cancer.

Chronic inflammation preceding PCa onset or cooperating with early stages of PCa development can be an essential source for new biomarkers that can be used in combination with PCs or other relevant cancer cell-derived factors. Such biomarkers can be released by immune cells in TME, or can be identified in circulating immune cells, in particular in monocytes. We have previously demonstrated that monocytes provide clinically valuable information for patients with breast and colorectal cancer [1–3]. In breast cancer CD163+ CD14^{low}CD16+ and CD163+ CD14+CD16+ monocytes were indicative for the presence of the malignancy, and CD14^{low}CD16+HLA-DR+monocytes were predictive for the good response to neoadjuvant chemotherapy [111]. In colorectal cancer (CRC), the monocyte biomarkers showed distinct correlations with metastatic processes [112]. Increased levels of CCR2+ monocytes in rectal cancer was indicative for the absence of both lymphatic and hematogenous metastasis. In contrast, in patients with colon cancer CD163+ monocytes positively correlated with lymphatic [112]. In this study we also made full transcriptome profiling in circulating monocytes by NGS, and identified PFKFB3, activator of glycolysis that is currently an attractive candidate for several solid cancers [112]. PFKFB3+ monocyte-derived macrophages massively infiltrated tumor in colon, and Nanostring spatial profiling identified correlation of PFKFB3 with tumor-promoting properties of TAMs in colon but not in rectal cancer. Monocytes-expressed PFKFB3 was indicative for tumor relapse specifically in colon but not rectal cancer [112]. Monocytes are not only indicators of the systemic immune status, but can be also programmed by systemic changes caused by all types of anti-cancer therapy: surgery, radiotherapy, chemotherapy and immunotherapy [113]. In cardio-metabolic disorders, monocytes are crucial biomarkers predicting progression of vascular complications related to the pathological lipid metabolism, and key role of monocyte-derived foamy macrophages

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is established [114–116].Considering recently identified by us and other foamy macrophages in PC, the potential of circulating monocytes as predictors of therapy efficiency and biomarkers that can be used for the personification of therapeutic schemas is only emerging but has solid theoretic background. For PCa the clinical value of monocytes programming and subpopulations urgently needs to be identified.

5. Methods for diagnosing prostate cancer.

5.1. Currently used diagnostic approaches

Clinical guidelines from various countries and leading cancer societies recommend similar algorithms for the diagnosis of PCa [108], [109], [117]:

- digital rectal examination (DRE)
- and/or transrectal ultrasound (TRUS)
- serum PSA (prostate-specific antigen): total PSA and the ratio of free PSA to total PSA.
- biopsy confirmation.

Table 3 summarizes the information about the sensitivity (the ability of the test to correctly identify patients with the disease) and specificity (the test's ability to correctly identify patients without the disease) of the PCa tests available for clinical appellation.

Tumor biopsy testing for somatic gene mutations (e.g., *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, and *CHEK2*), MSI, or dMMR should be considered as additional diagnostic options for patients with regional or distant metastases [108]. Table 3 summarizes data on the sensitivity and specificity of each type of diagnostic method, and their advantages and disadvantages. Each type of test has limitations and can miss a case of prostate cancer; only the combination of several tests provides the most complete picture. The maximal sensitivity of a single text is not exceeding 77%, and the maximal specificity of a single test is below 50%. Therefore, it is necessary to improve the test systems or their combination to prove precise clinical decision.

5.2. Necessity of early screening

Early PCa can be asymptomatic, so screening is necessary. The gold standard for screening now are PSA testing and Digital Rectal Examination [109, 110]. Since the introduction of the PSA testing and subsequent biopsies, the incidence of PCa in the USA doubled, beginning in the late 1980s [113, 114]. The UK interview study used EPIC-26 questionnaire to analyze 3 523 patients 18-42 months after they were diagnosed for prostate cancer. This study revealed that quality of life is higher in patients diagnosed with PSA-screened PCa compared to patients diagnosed due to symptoms of PCa [120].PCa was detected through PSA testing in 31.3% of cases, while it presented with symptoms in 59.7% of cases. In a multivariate analysis, men with symptoms reported more severe problems with urinary incontinence (Adjusted mean ratio (AMR): 0.96, 95% CI: 0.96-0.97), bladder irritation (AMR: 0.95, 95% CI: 0.95-0.96), bowel function (see AMR: 0.97, 95% CI: 0.97-0.98), sexual function (AMR: 0.90, 95% CI: 0.88-0.92), and vital/hormonal function (AMR: 0.96, 95% CI: 0.96-0.96 compared to men whose PCa was found via the PSA test. These differences were consistent among respondents of different ages, stages, Gleason scales, and treatment types [120].

Early detection of PCa improves overall patient survival in low-risk patients, but has no effect on the survival of patients with metastatic cancer [115–117]. Since the management strategy for low-risk patients is an active monitoring, careful patient selection and accuracy in risk assessment require new more precise and more specific biomarkers, since randomized controlled trials have shown that PSA screening has no effect on overall mortality or prostate cancer–caused mortality [123]. A meta-analysis of five randomized controlled trials involving 721,718 men found that screening probably leads to a small reduction in specific mortality over 10 years, but has no effect on overall mortality [124]. It has no effect on all-cause mortality (IRR 0.99, 95% CI 0.98-1.01) and may have no effect on

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prostate-specific mortality (IRR 0.96, 0.85-1.08;), or a small effect on prostate-specific mortality (IRR 0.79, 0.69-0.91). Using Der Simonian and Laird's inverse of variance random effects modeling , it was estimated that for every 1,000 men screened, about 0,1% will be hospitalized because of biopsy complications, 0,3% will have reduced quality of life because of bladder control problems, and 2,5% will have erectile dysfunction [124]. In addition to the side effects caused by screening procedures, it is necessary to consider the patient's psychological discomfort due to false positive PSA tests.

There is also evidence of the benefits of measuring baseline PSA levels in men in middle age to determine the subsequent risk of PCa [125]. Analysing 13 years of data from a cohort of 10,968 men between the ages of 55 and 60 included in the PCa screening group showed baseline prostate-specific antigen levels were associated with any future prostate cancer. The risk was significantly lower among men with baseline prostate-specific antigen levels less than 2.00 ng/mL [126].

From the standpoint of reducing mortality, overtreatment, which refers to unnecessary or excessive medical interventions, offers little or no benefit. Many years after treatment with radical prostatectomy or radiation therapy for high-risk prostate cancer, a significant proportion of men still have significant deterioration in one or many functional areas: sexual, urinary, and intestinal function [7, 121–123]. Modeling of the lifelong consequences of annual PSA screening at the age of 55-69 years compared with the absence of screening estimated the loss of 23% of the years of life obtained during screening, mainly due to deterioration in the quality of life due to long-term side effects from treatment [125].

The study covered a cohort of 182,160 men aged 55 to 69 from eight European countries calculated the number of men that have to be invited for screening to prevent one death from PCa [129]. They used the Wald method to calculate confidence intervals for the difference in the risk of death.The result of this calculation demonstrated that prevention of one death prom PC requires screening of PSA levels for 9 years in 1947 men, for 13 years in 742 men, and for 16 years in 570 men [129].

5.3. Biopsy examination and how TAMs can help

Prostate biopsy is a medical procedure used to diagnose prostate cancer. It involves the removal of a small tissue sample from the prostate gland, which is then examined under a microscope for the presence of cancer cells. To assess the degree of differentiation prognostically, pathologists evaluate PCa biopsies. When examining biopsy samples, an assessment is made of the shape, size of cells, nuclear changes, and the presence of anomalies in cellular structure [130]. Additionally, the degree of differentiation of cancer cells is evaluated. Furthermore, the quantity and distribution of cancer cells in the sample, as well as the presence of invasion into surrounding tissues, are assessed. This helps to determine the stage of PCa and its potential for spread or metastasis [130].

The histological evaluation of PCa samples also includes a description of specific pathological features such as the presence of glandular structures, cribriform patterns, perineural invasion, and others. To unify the examination of samples, Donald Gleason developed a scale for evaluating the architectural details of malignant glands under at low and medium zoom [131]. According to the Gleason scale, microscopic estimation of histopathological features is used to classify cancerous tissue from low-differentiated (highest grade) to highly differentiated (lowest grade). In 2014, the classification system was reorganized into groups 1-5 according to the International Society of Urological Pathology (ISUP) classification [132]. The Gleason classification of acinar adenocarcinoma of the prostate is one of the earliest and most successful applications of evidence-based medicine in routine clinical practice. The original Gleason system has shown excellent correlation with clinical outcomes [128, 129].

The field of PCa diagnosis and treatment has witnessed significant advancements in recent years, with the development of several diagnostic tests based on new biomarkers. These tests aim to enhance the specificity and sensitivity of prostate-specific antigen (PSA) screening, while also improving treatment efficiency. In light of these advancements, it becomes increasingly crucial to

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consider the incorporation of newly identified biomarkers to further enhance diagnostic accuracy and optimize patient management.

Among the emerging biomarkers, the prostate health index (PHI), *TMPRSS2*-ERG fusion gene, 4K test, and PCA3 test have shown promising potential in PCa diagnosis [135]. The 4K test, for instance, utilizes a panel comprising total PSA (tPSA), free PSA (fPSA), intact PSA (iPSA), and human kallikrein 2 (hK2). By analyzing these biomarkers, it becomes possible to differentiate between various causes of elevated PSA values, offering valuable insights into the presence and characteristics of PCa [136]. Unbound PSA is known as free PSA (fPSA), which is about 5%-35% of total PSA. The investigation of different forms of PSA, such as free PSA (fPSA) and intact PSA (iPSA), has provided valuable information for the identification and stratification of prostate cancer. While fPSA represents the unbound fraction of PSA, accounting for approximately 5% to 35% of total PSA, iPSA demonstrates a higher ratio in men with cancer compared to those without tumors [117]. Furthermore, human kallikrein 2 (hK2), a closely related protein to PSA, has exhibited structural and functional similarities, offering additional insights into PCa detection[138]. These biomarkers will help to identify high-grade PCa in men who have not previously been tested for elevated PSA. The PHI (prostate health index) defined by the formula [([-2]proPSA / free PSA) × √total PSA] was developed for prognostic purposes [117, 119]. The PHI, compared to other PSA related tests, has been shown to better differentiate PCa from benign prostatic hyperplasia ,and thus to prevent unnecessary prostate biopsy [133, 135]. The PHI test allows to detect the progression of PCa with active monitoring of the condition. Additional non-invasive biomarkers used for diagnostic purposes are *TMPRSS2-ERG* Fusion and PCA3 Progensa PCa Antigen 3 based on urine [135]. One of the markers of castrate resistance in PCa is the level of *TMPRSS2-ERG*. Serine protease 2 (TMPRSS2), as well as the *ERG* gene, can be found in 50% of patients with prostate cancer, overexpression of the PCA3 or *DD3* gene (specific non-coding mRNA) is observed in more than 95% of cases of primary PCa [141]. However, the assessment of the above markers in comparison with the prostate specific antigen has a lower sensitivity. The accuracy of PCa biomarkers is critical in determining the further tactics - the transition to invasive methods of examination [141].

As can be seen from the above, the accuracy of PCa biomarkers is critical in determining the further tactics - the transition to invasive methods of examination. Deciding the necessary of screening, it is needed to take into account and individually discuss the strategy with transgender patients taking or not taking hormone therapy, since the risk of PCa for them has not been determined [137, 138]. However, the biopsy examination in the current clinical practice does not consider evaluation of any immunological parameter in tumor microenvironment. Tumor-associated macrophages massively infiltrate solid tumors, and in several cancers, including prostate cancer, bad prognosis correlates with increased amounts of TAMs, identified in majority of studies by highly specific macrophage marker CD68, that belongs to scavenger receptor family [144].

However, there are also cancer types or specific intertumoral compartments, where levels of CD68+ TAMs in parenchima in breast cancer have a negative correlations with lymphatic metastasis, and in colorectal cancer total CD68 levels positively correlate with overall survival and good prognosis [144–146]. Therefore number of studies are focusing o the specific TAM biomarkers, there scavenger/endocytic receptors for example CD206, stabilin-1, MARCO and others) demonstrated specific correlations with stages, metastasis and even therapy responses for lung, breast, colorectal, ovarian, prostate and other types of cancer [144]. However, scavenger receptors (SRs) are limited in the demonstrating of specific TAM functional polarization to high redundancy of SRs' ligand repertoire and functions [147]. More specific biomarkers with clear distinct functions are needed to distinguish between tumor-promoting and anti-tumor TAMs. Chitinase-like proteins, potent regulators of angiogenesis and immune cell recruitment can offer here much more precise biomarker value [148, 149]. Metabolic regulators, as we identified for colorectal cancer, is also of a great potential [112]. In case of prostate cancer, we have observed even on the morphological level 2 major phenotypes of TAMs: regular in size and shape, and large foamy-types TAMs [150]. Identification of the molecular profile and functions of these 2 major phenotypes of TAMs is needed to decipher their biomarker potential.

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The limited integration of these new biomarkers in routine clinical practice can be attributed to several factors. Further validation and standardization across different populations and settings, cost-effectiveness, and accessibility challenges, as well as interpretational complexities, hinder their widespread use. The reliance on PSA as the primary screening tool and the need for a shift in established practices also contribute to their limited utilization. Continued research, standardization efforts, and evidence-based guidelines are crucial for facilitating their integration into PCa care.

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Table 3. Diagnostic procedures for prostate cancer according to the international clinical guidelines [108], [109].

Diagnostic method	Principle	Sensitivity (0-1)	Specificity (0-1)	False-negative cases (%)	False positive cases (%)	Benefits	Limitations	Reference
Digital Rectal Examination (DRE)	Palpation of the lower part of the rectum, pelvis and lower abdomen	0,51	0,59	-	-	availability and affordability non-invasive	low sensitivity lack specificity More than 60% are identified as asymptomatic	[118, 139, 140]
Prostate Specific Antigen (PSA)	Venous blood sampling for prostate-specific antigen, a glycoprotein expressed in both cancerous and normal columnar prostate epithelial cells.	0,21-0,5	0,91	10-15%	-	availability and affordability	lack specificity predictive accuracy of 8% to 10%	[118, 141, 142]
Transrectal Ultrasound Scan (TRUS)	Ultrasound examination of the prostate with insertion of the sensor into the rectum.	-	-	11,34-29,31	4,61-6,11%	availability and affordability non-invasive	lack specificity	[123]
Transrectal biopsy (TRB)	Tissue sampling with a thin needle that is inserted through the rectum into the prostate.	0,53	1	11-46%	-	Availability affordability	most lesion are small and sometime located in regions that are not identifiable Complications of prostate biopsy (eg, infection, pain, bleeding, urinary obstruction)	[118, 139, 143–146]

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MRI -guided biopsy	MRI-guided sampling of prostate tumor tissue	0.77	1	6%	4,2%	accuracy	Complications of prostate biopsy (eg, infection, pain, bleeding, urinary obstruction); expensive	[143–145]
MRI	Creation of detailed volumetric images of areas using a magnetic tomography	0.67	0.92	2,7%	44,1%	non-invasive	expensive	[143, 145]

"-" no data available

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5.4. State-of-the art imaging for staging and metastasis detection

A multicenter, paired-cohort, confirmatory study was conducted to test the diagnostic accuracy of MP-MRI and TRU-biopsy [159]. A total of 740 men with prostate-specific antigen concentrations up to 15 ng/mL, without prior biopsy, who underwent MRI followed by TRU biopsy were included in the study. The performance and reporting of each test was blinded to the results of the other tests. Clinically significant cancer was defined as a Gleason score ≥4 + 3. For clinically significant cancer, MP-MRI was more sensitive (93%, 95% CI 88-96%) than TRUSI biopsy (48%, 42-55%; p<0-0001) and less specific (41%, 36-46% for MP-MRI versus 96%, 94-98% for TRUS biopsy; p<0-0001). 44 (5-9%) of 740 patients reported serious adverse events, including 8 cases of sepsis [159].

Modern imaging techniques (CT, MRI, PET) can accurately determine the presence of metastases and the stage of development of PCa. MRI with high accuracy can reduce the number of unnecessary biopsies compare with standard TRUS. PI-RADS was introduced by the European Society of Urogenital Radiology to standardize the results of MRI. Key elements of assessment include prostate volume measurement, lesion mapping, lesion measurement, and lesion assessment [160].

However, the high cost and low availability of these methods is an obstacle to accurate diagnosis (Table 2)

5.5. Raman spectroscopy

One of the advanced optical diagnostic methods is the Raman spectroscopic analysis, the use of which is acceptable in the study of tissues and / or biofluids for in vitro and in vivo diagnostics. Raman imaging provides real-time results, contributing a molecular portrait of tissue in malignant diseases such as prostate cancer. The basic principle of Raman spectroscopy is associated with the interaction of light with the molecules of substances contained in the analyzed samples [161]. Raman spectroscopy has been positively evaluated as a diagnostic method for differential analysis of malignant and non-malignant tumors of the prostate tissue. Aubertin et al. conducted a study of 32 fresh prostatectomy tissue samples with Raman spectroscopy to detect and analyze the severity of PCa [162]: from samples of fresh prostate tissue, sections were obtained, from each of which 20 to 50 scattering spectra were obtained, the total number of which was 947 spectra. Using Raman spectroscopy, it was found that the sensitivity in identifying the prostate among non-prostatic tissue was 82%, the specificity was 83%. During the analysis, it was also noted that the method made it possible to distinguish benign prostate tissue from malignant tissue with a sensitivity of 87% and a specificity of 86% [162]. Pinto et al incorporated Raman spectroscopy for in vivo (n = 4) and ex vivo (based on 599 spectra from 20 prostatectomy specimens) into the operational process of robotic radical prostatectomy to differentiate between cancerous and benign prostate tissue [163]. A study by Medipalli et al. compared the Raman spectra of plasma from 43 patients diagnosed with PCa and 33 healthy volunteers. As a result, it was found that in the plasma of patients with prostate cancer, during the interpretation of Raman spectra, an increase in the bands associated with nucleic acids was revealed [164]. In interpreting the results, it is worth noting that the increase in nucleic acid concentration may be associated with abnormally increased gene expression, which correlates with increased release of nucleic acids due to cell death. In patients diagnosed with prostate cancer, compared with healthy people, absorption bands corresponding to lipids are more common. This may be due to the fact that the risks of tumor progression and treatment resistance are associated with high levels of lipids and cholesterol in the tumor [165, 166].

Raman spectroscopy is a minimally invasive analysis technique that can be used to analyze samples of urine, blood, saliva, and other body fluids. Del Mistro et al. conducted an experimental surface-enhanced Raman scattering (SERS) analysis of urine samples from 9 patients diagnosed with PCa and 9 healthy volunteers. Using machine learning algorithms, the obtained spectra were divided into two groups (PCa or healthy people), resulting in a sensitivity of the analysis of 100%, a specificity of 89% [167]. Similarly, Ma et al. used SERS to obtain urine spectra of 75 patients, of which 12 patients with recurrent PCa and 63 patients with non-recurrent PCa [168]. While comparing Raman bands in

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patients without recurrence and with recurrent prostate cancer, it was found that the latter have enhanced Raman bands associated with lipids, proteins, amino acids and DNA [168]. Review by Chen et al. demonstrates the most complete information about Raman scattering methods based on urine [169] . Serum measurement of prostate specific antigen (PSA) protein is the most common method for identifying men at risk of developing prostate cancer, but the PSA test has certain limitations due to type I errors [153]. False elevated PSA can be observed with prostatitis, benign prostatic hyperplasia, urinary tract infections [154]. In men, PSA levels in the 4–10 ng/mL range represent a significant diagnostic challenge, Chen et al. investigated the use of serum SERS as a screening method to differentiate between PCa and BPH in patients with above-specified PSA levels [170].

Raman imaging techniques allow specific identification of individually pure substances, often without the need for contrast agents. This represents great promise for in vivo applications in disease diagnosis, treatment outcome monitoring, disease prognosis, and disease staging. By developing special nanoparticles in the SERS process, it is possible to achieve high sensitivity and specificity for diagnostic purposes in various biological fluids.

6. Conclusions

In conclusion, the current limitations of clinical and pathological parameters in accurately differentiating prostate cancer types present a significant obstacle in preventing unnecessary treatments. The application of modern molecular genetic techniques has provided an opportunity to gather comprehensive data encompassing genomic, transcriptomic, epigenomic, proteomic, and metabolomic profiles from various sources such as biopsies, prostatectomies, and individual cells. The integration of these data into clinical practice is of utmost importance [7]. However, each tumor develops in the close contact with the immune system, both systemic and local, where the immune system can be 1) pre-programmed to be more cancer permissive or restrictive; 2) programmed by growing tumor; 3) programmed by cancer therapy. Such programming can be be on epigenetic, transcriptional and metabolic levels, and each level can offer clinically applicable [111, 171]. Thus, the immune biomarkers, in particular biomarkers provided by innate immunity(circulating monocytes and TAMs), is essential to significantly enhance the precision of the diagnostics and to achieve maximal therapeutic efficacy.

By harnessing this wealth of information, we can gain a better understanding of the disease's variability and tumor progression, thereby identifying valuable biomarkers for effectively managing newly diagnosed cases and tailoring treatment strategies to individual patients. This approach holds great promise in optimizing prostate cancer care and ensuring that patients receive the most appropriate and personalized treatments.

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Abbreviations

21-kDa protein
BAD Bcl-2 agonist of cell death
Bcl-2 - family of regulator proteins that regulate cell death (apoptosis), by either inhibiting (anti-apoptotic) or inducing (pro-apoptotic) apoptosis
Bcl-xL It is a member of the Bcl-2 family of proteins, and acts as an anti-apoptotic protein.
Bmi-1 Polycomb complex protein BMI-1
cAMP responsive element binding protein (CREB)
CASP9 - caspase 9
CBP CREB-binding protein
CDKN1B cyclin dependent kinase inhibitor 1B

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CDK2 - cyclin dependent kinase 2
ERK extracellular signal-regulated kinase
FKHR - a subfamily of "forkhead" proteins that regulate transcription.
FOXA1 s a transcription factor (TF) of the Forkhead box (FOX) protein family.
GFR - growth factor receptors
GF - growth factor
Grb2 Growth Factor Receptor bound 2
GSK-3 Glycogen synthase kinase 3
GSTP1 - glutathione S-transferase pi 1
HIV - human immunodeficiency virus
HCs-96
HOX subset of homeobox genes, are a group of related genes that specify regions of the body plan of an embryo along the head-tail axis
HRas proto-oncogene Harvey-RAS
IL1R2 - interleukin 1 receptor type 2
IKK IκB kinase
IκB [I-kappa-B], a protein complex
MSI microsatellite instability
MDM2 proto-oncogene encodes a nuclear-localized E3 ubiquitin ligase.
MEK Mitogen-activated protein kinase - MAPK/ERK (MAPK/ERK kinase *или* MEK MAPK mitogen-activated protein kinase ERK extracellular signal-regulated kinase
MMP Matrix metalloproteinases
mTOR mammalian target of rapamycin
NF-kB Nuclear Factor Kappa B
NKX3-1 NK3 homeobox 1
NBS1 - is a protein which in humans is encoded by the NBN gene
p21 wildtype activating factor-1/cyclin-dependent kinase inhibitory protein-1 or WAF1/CIP1
P27 - tumor suppressor, inhibit all types of cyclin-dependent kinase (cyclin dependent kinase CDK)
P53 protein regulates the repair of cellular DNA.
PDK1 - Phosphoinositide-dependent kinase-1
PI3K phosphatidylinositol-3-kinase
PIP3 - phosphatidylinositol-3,4,5-triphosphate
pkb/akt - protein kinase B
PLAU plasminogen activator, urokinase
PLAT (tissue plasminogen activator)
PSA prostate specific antigen
RNase L (HPC1) interferon (IFN)-induced ribonuclease which, upon activation, destroys all RNA within the cell (both cellular and viral)
Rb - Retinoblastoma protein
SRD5a2 - Steroid 5-α-reductase type 2
SPINT1 - serine peptidase inhibitor, Kunitz type 1
TCF/LEF The TCF/LEF family (T cell factor/lymphoid enhancer factor family)
TMPRSS2 - Transmembrane serine protease 2
TMPRSS2-ERG - fusion of transmembrane serine protease 2 (TMPRSS2) genes with ETS transcription factor
TF Tissue factor
TRBP transactivation response element RNA-binding protein

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