

## REVIEW

# Prostate cancer research in China

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Prostate cancer (PCa) research in China has been on a rocketing trend in recent years. The first genome-wide association study (GWAS) in China identified two new PCa risk associated single nucleotide polymorphisms (SNPs). Next generation sequencing is beginning to be used, yielding novel findings: gene fusions, long non-coding RNAs and other variations. Mechanisms of PCa progression have been illustrated while various diagnosis biomarkers have been investigated extensively. Personalized therapy based on genetic factors, nano-medicine and traditional Chinese medicine has been the focus of experimental therapeutic research for PCa. This review intends to shed light upon the recent progress in PCa research in China and points out the possible breakthroughs in the future.

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## INTRODUCTION

Prostate cancer (PCa) is currently the second most frequently diagnosed cancer worldwide, causing 258 000 deaths annually.<sup>1</sup> Although the incidence of PCa in China was reported to be 1.6/100 000 per year, ranking one hundred seventieth among all nations,<sup>2</sup> its incidence in China has recently increased substantially,<sup>3</sup> with an estimated incidence of 10/100 000 in 2010 compared with 1.71/100 000 in 1993.<sup>4</sup> With the implementation of more comprehensive screening programmes in China, the incidence rate of PCa may rapidly increase in the future.

The number of PCa research projects by Chinese investigators has increased substantially in recent years. Led by those institutes with notable achievements, the quality of published articles by Chinese investigators is also increasing. The number of published studies doubled from 2008 to 2012; however, the number of citations to these studies increased considerably from about 300 to about 8000 (statistics from the Web of Science). Novel technologies, such as genome-wide association study (GWAS) and next-generation sequencing, are beginning to be used in China, yielding notable achievements in elucidating the aetiology, mechanisms of progression, diagnostic biomarkers and therapeutic targets of PCa. This review highlights recent progress and discusses possible future breakthroughs in PCa research in China.

## MAJOR ACHIEVEMENTS

### Chinese GWAS in PCa

Recently, through the joint efforts of a number of researchers, we reported the first GWAS in Chinese PCa patients.<sup>5</sup> This is the first confirmation of the unique characteristics of Chinese PCa in a large population. A total of 4484 PCa patients and 8934 healthy controls were involved in the study, and two new loci, 9q31.2 and 19q13.4, were found to be significantly associated with PCa risk. The rs103294 marker at 19q13.4 is in strong linkage equilibrium with a 6.7-kb germline deletion that removes the first six of seven exons in *LILRA3*, a gene regulating the inflammatory response, and is significantly associated with the mRNA

expression of *LILRA3* in T cells. Our study provides the first evidence of a genetic difference between Chinese and Caucasian PCas.

Several Chinese researchers have investigated the underlying mechanisms by which single-nucleotide polymorphisms (SNPs) are involved in prostate tumourigenesis. Lu *et al.*<sup>6</sup> utilized ChIP-on-chip analyses to demonstrate that regions containing androgen receptor (AR)-binding sites are significantly enriched for PCa risk-associated SNPs. It has also reported that one-third of the reported 33 genes in the Caucasian GWAS are AR-related. The findings suggest that some PCa-associated SNPs act through an androgen-mediated mechanism to influence PCa risk.<sup>6,7</sup>

Although confirmation and functional research based on Chinese GWAS are ongoing, GWAS and their potential applications have not yet been fully explored. Discovering the biological and clinical significance of GWAS results has been a new arena for those enthusiastic scientists. Studies have shown that SNPs can help to increase the positive prediction values for patients who intend to undergo prostate biopsies, significantly reducing the number of unnecessary biopsies.<sup>8</sup> Furthermore, SNPs showed great value in the field of pharmacogenomics and personalized medicine. For advanced renal-cell carcinoma patients undergoing first-line sunitinib therapy, similar personalized therapies will be offered soon. Researchers have found two SNPs that are correlated with decreased sunitinib response and tolerability.<sup>9</sup> For patients with these genetic polymorphisms, it would be advantageous to take decreased doses or to forgo this therapy completely. Further studies on PCa and the sunitinib research should be carried out to offer personalized treatments.

### Gene fusion

The gene fusions between transmembrane protease serine 2 (TMPRSS2) and E26 (ETS) transcription factors are cancer-specific biomarkers in PCa, and such fusions are the most common genetic events in PCa, accounting for 90% of PCa fusions.<sup>10</sup> Since the first report of PCa gene

fusion in 2005, its role in diagnosis has been extensively studied.<sup>11</sup> According to a multicentre study in North America, the prevalence of TMPRSS2-ERG gene fusion is 46% in patients undergoing biopsies.<sup>12</sup> In Chinese PCa patients, we carried out an RNA sequencing test that revealed variation in the transcriptome and indicated a much lower prevalence of TMPRSS2-ERG. Only 21.4% and 18.5% of patients in the discovery and validation periods harboured this variation.<sup>13</sup> Such findings are consistent with previous reports on PCa patients in China,<sup>14</sup> as well as those in Japanese and Korean populations.<sup>15–17</sup> Two novel gene fusions, CTAGE5-KHDRBS3 and USP9Y-TTTY15, occurred frequently in our patient cohort;<sup>13</sup> further validation in a larger and multi-centre population is warranted. These differences may be further utilized in exploring the unique Chinese mechanism upon tumour onset and progression, as a study has confirmed a possible alternative path of carcinogenesis in gene fusion and PTEN inactivation.<sup>18</sup>

The occurrence of rearrangements has been explained by the following genomic, cellular and environmental changes: spatial proximity, cellular stress, inappropriate repair or recombination, and DNA sequence and chromatin features.<sup>19</sup> The differences between Chinese and Western patients may be explained by the difference in one or more of these changes. Potential environmental differences include variation in red meat intake and in genetic backgrounds, which influence AR sensitivity. Interaction between genetic and environmental factors most likely contributes to the differences over a long and complex transition.

#### Diagnostic biomarkers and improved imaging technologies

Although prostate-specific antigen (PSA) has been the epoch-making marker for PCa screening and diagnosis, it is not perfect. Advances in DNA and RNA sequencing have enabled diagnostic markers to enter the era of ‘-omics’.<sup>20</sup> SNPs, PCA3, microRNAs, PSA isoforms, long non-coding RNAs and TMPRSS2-ERG gene fusion are under extensive investigation.

Chinese researchers used a panel of 33 SNPs to calculate a genetic score as a diagnostic factor in a Chinese population, which showed a significant difference between the results of patients with PCa and healthy controls.<sup>21</sup> The area under the curve for the genetic score was 0.604 for the risk prediction of PCa. Another study further combined the protein-based and metabolite-based factors in urine as a useful model for diagnosis. The expression patterns of PCA3, TMPRSS2-ERG, Annexin A3, Sarcosine and a panel including these biomarkers were significant predictors of PCa both in patients with PSA 4–10 ng ml<sup>-1</sup> and in all patients.<sup>22</sup> Using an Illumina miRNA microarray, Chinese researchers identified five possible microRNAs with the ability to differentiate among healthy, benign and cancerous prostates.<sup>23</sup> Our group found that intron 4 retention in PSA and exon skipping in AMACR were highly specific for PCa. Both the alternatively spliced transcripts and the proteins may serve as new potential diagnostic biomarkers for PCa.<sup>24</sup>

New imaging technology has improved PCa detection. It has been reported that contrast-enhanced ultrasonographic microflow imaging could significantly improve the detection accuracy rate of PCa in men with PSA values 4–10 ng ml<sup>-1</sup> greater than conventional ultrasound.<sup>25</sup> The sensitivity, specificity and accuracy were 70.3%, 82.5% and 80.3%, respectively. Another study challenged conventional computed tomography and magnetic resonance imaging using susceptibility-weighted imaging.<sup>26</sup> Susceptibility-weighted imaging was demonstrated to detect a greater number of prostate haemorrhages than computed tomography and magnetic resonance imaging and was better able to distinguish PCa from benign prostatic hyperplasia. Novel imaging

technologies can and likely will soon offer more accurate diagnoses as a result of rapid technological innovation, such as molecular imaging.

#### Mechanism of PCa progression

The progression of PCa is mainly related to two events: metastasis and the development of castration-resistant prostate cancer (CRPC). Although the mechanism of metastasis has been elucidated in various ways and a number of new drugs for CRPC have been approved by the FDA, the development of metastasis and the formation of androgen-independent states remain tough issues to face in the clinic. Proteomic analysis has been used to detect metastasis-related proteins in PCa and showed that 58 proteins are differently expressed in lymph node-metastatic PCa, compared with localized PCa. Six of these protein expression patterns, including the increased expression of e-FABP5, MCCC2, PPA2, Ezrin and SLP2 and the decreased expression of SM22, have a functional relation to PCa progression.<sup>27</sup> HoxB3 was found to promote PCa progression by transactivating CDCA3.<sup>28</sup>

CRPC is the result of the regrowth of PCa cells that have adapted to the hormone-deprived environment of the prostate. Many studies have focussed on CRPC progression and analysed the process from different angles; however, there is no simple answer to this question. Tissue PSAs may activate AR by enhancing the expression of ARA70, resulting in an androgen-refractory PCa.<sup>29</sup> In accord with these findings, 5-aza-2'-deoxycytidine, which can effectively inhibit the methylation of the AR promoter, was reported to be an effective agent in the suppression of refractory progressions.<sup>30</sup> Changes in miRNA are also involved in the progression of CRPC.

High-throughput Illumina sequencing was applied to find that some miRNAs are upregulated whereas others are downregulated in androgen-independent cell lines; this finding suggests that these miRNAs may be involved in the transition of LNCaP to an androgen-independent phenotype.<sup>31</sup> In investigating long, non-coding RNAs, we found a total of 137 long non-coding (nc) RNAs that were consistently upregulated or downregulated in PCa patients. We have confirmed two known lncRNAs and identified three novel long ncRNAs, namely, FR0257520, FR0348383<sup>32</sup> and PlncRNA-1,<sup>33</sup> that are significantly associated with PCa. We postulate that long ncRNAs may have functions beyond transcriptional regulation, as PlncRNA-1 suppression resulted in a decrease of AR mRNA, proteins and AR downstream targets. This result suggests a reciprocal regulation of PlncRNA-1 and AR, revealing PlncRNA-1 as a potential therapeutic target for PCa.

#### Therapeutic approaches

Several therapeutic explorations aimed at three main aspects have been carried out: personalized therapy based on genetic factors, nanomedicine and traditional Chinese medicine. Future treatment approaches will utilize more specific and more personal treatment. Thalidomide has been tested in phase III trials for treating CRPC without satisfactory results. Some patients have a positive outcome to thalidomide treatment, but others do not respond at all. A possible explanation for the different responses to thalidomide, which we showed experimentally, is that sensitivity to thalidomide is positively correlated with CUL4A expression in a panel of prostate cell lines. CUL4A is a potential drug target of thalidomide, and high CUL4A expression is correlated with the effectiveness of thalidomide.<sup>34</sup>

In addition, several studies have focussed on biomarkers that can predict responses to docetaxel treatment in PCa. Chemosensitivity to

docetaxel in three prostate cell lines has been demonstrated to be enhanced with the knockdown of p21-activated kinase 6. The knockdown of p21-activated kinase 6 expression caused an inhibitory effect on PCa growth and enhanced chemosensitivity to docetaxel.<sup>35</sup> In addition, miR-21 was found to be upregulated in docetaxel-resistant cell lines, suggesting that miR-21 contributed to this resistance to docetaxel.<sup>36</sup> In the future, these targets may serve as promising therapeutic approaches in sensitizing PCa to docetaxel treatment. Regarding the use of adjuvant therapy for PCa patients, a group of researchers identified two PCa susceptibility variants, rs16901979 and rs7931342, as prognostic predictors for survival after androgen-deprivation therapy. These variants are associated with disease progression, PCa-specific mortality and all-cause mortality. This finding allows for the identification of high-risk patients who might benefit from appropriate adjuvant therapies after radical prostatectomy.<sup>37</sup>

Led by Xin Gao from the Third Affiliated Hospital of Sun Yat-sen University, investigators have tested nanoparticles intergraded with chemical active substances as promising imaging and therapeutic tools. Docetaxel-loaded oleic acid-coated hydroxyapatite nanoparticles can enhance the apoptosis of androgen-independent PCa cells by activating caspase-2.<sup>38</sup> Another nanoparticle intergraded with docetaxel and superparamagnetic iron oxide showed both stable superparamagnetic behaviour and antiproliferative effects in PC3 cell lines.<sup>39</sup> Moreover, previous studies have implemented a covalent layer-by-layer particle that is conjugated to a single-chain prostate stem cell antigen antibody and that can realize the targeted delivery to PCa, offering a sustained release pattern in mice.<sup>40</sup> Although study of these nanoparticles is still in the preliminary period, these nanoparticles have great potential for imaging and chemotherapy, considering the continuing improvements in nanotechnology.

Traditional Chinese medicine, the treasures left by our ancestors, is effective in combating cancer, but no specific mechanism has been identified. However, novel technologies may allow for the potential of components of traditional Chinese medicine as antitumour drugs to be elucidated. A group led by Mingyao Liu from East China Normal University has focussed on several components of traditional Chinese medicine as potential antitumour drugs that target different signalling pathways and inhibit tumour angiogenesis. Cucurbitacin E,<sup>41</sup> plumbagin<sup>42</sup> and acetyl-11-keto-beta-boswellic acid<sup>43</sup> inhibit tumour angiogenesis by targeting the Vascular Endothelial Growth Factor Receptor 2 (VEGFR2)-related signalling pathway, while kisspeptin-10<sup>44</sup> suppresses Sp1-mediated vascular endothelial growth factor expression and FAK/Rho GTPase activation. Since angiogenesis plays an important role in tumourigenesis, progression and metastasis, these components may act as a promising target therapy; still, more clinical trials should be carried out. Further, genistein, a major isoflavone constituent of soybeans, has been demonstrated to have anti-cancer effects. Researchers have found that genistein can effectively inhibit the transition of PCa cells from epithelial to mesenchymal, as well as their stemness properties.<sup>45</sup>

## FUTURE DIRECTION

During the past few years, the Chinese public and government are beginning to pay more attention to PCa and have attached great importance to basic research related to PCa, especially translational research. Governmental funding for PCa research has increased consistently, including the first National Basic Research Program of China (973 Program). Chinese scientists now face unprecedented opportunities and challenges. As mentioned above, novel gene fusions, copy number variances and long ncRNAs have been discovered in the

Chinese population. The vast discrepancy in prevalence of PCa between Chinese and Caucasian populations, as well as differences in each oncological pathway, urgently needs to be elaborated. Furthermore, it is hoped that in the near future, a Chinese PCa research cooperation network, including patient databases with concrete information and abundant patients, will be established. The results of GWAS should be extensively interpreted in the field of pharmacogenomics to identify better biomarkers for predicting drug efficacy and toxicity. Finally, next-generation sequencing may open a new window to a greater understanding of this disease, particularly in the Chinese population.

## AUTHOR CONTRIBUTIONS

YHS provided original ideas and instructed the writing of this article. SCR and RC searched and summarized the literature. SCR and RC also wrote the manuscript.

## COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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