

## New discoveries in prostate cancer pathogenesis

### Novosti pri patogenezi raka prostate

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**Background.** Through PSA screening the rate of prostate cancers detected at an early stage has increased significantly; thus a decrease in mortality can be expected in the near future. Despite all scientific efforts, however, the molecular mechanisms underlying the development and progression of prostate cancer remain poorly understood. Prostate cancer is a disease of aging men and epidemiological evidence supports a major contribution to its development through diet, lifestyle and environmental factors.

Genetic instability is the basic phenomenon of tissue cell cancerisation. This instability can be hereditary or due to mutations and other chromosomal aberrations acquired during life. In recent years a large number of interesting data have been collected which show the relationships between focal atrophy and genetic instability of the prostate epithelia. Atrophy can be the result of prostatitis, ischemia as well as of oxidative stress (diet). Several chromosomal aberrations typical for prostate cancer (loss of 8p22; gain of 8q24 and X) can be already detected in the epithelia of the atrophic areas. Moreover also the deactivation of a gene (GSTP1) which encodes a carcinogene-detoxification enzyme has been found in such epithelia.

**Conclusions.** Molecular pathology is slowly revealing the links which exist among age, atherosclerosis and oxidative stress (diet), inflammation and the pathogenesis of prostate cancer. In the near future perhaps this knowledge will enable us to actively prevent this most common malignancy of elderly men.

*Key words:* prostatic neoplasms – diagnosis – therapy; pathogenesis

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**Izhodišče.** Rak prostate je trenutno najpogostejši zlohotni tumor moških, ki so starejši od 50 let. S PSA (prostata specifični antigen) presejanjem seveda število novih obolenj, ki so diagnosticirana v zgodnjem, ozdravljivem stadiju, stalno narašča, unrljivost pa bo začela že v bližnji prihodnosti vidno padati. Vkljub temu, da se veliko število raziskovalcev po celem svetu posveča raku prostate, ostajajo problemi njegove etiopatogeneze še vedno nerešeni in skrivnostni. Epidemiološke študije kažejo, da so vzroki nastanka tega raka verjetno združeni s starostjo, prehrano, življenjskimi navadami (life style) in tudi z neznanimi eksogenimi dejavniki.

Destabilizacija genetskega materiala v celicah je osnovni fenomen pri nastajanju raka. Destabilizacija je lahko prirojena ali pa jo povzročajo mutacije kromosomov, ki nastajajo tekom življenja. Novejše znanstvene raziskave kažejo, da destabilizacija genov začinja že z acinarno atrofijo, ki je lahko posledica vnetja, prekrvavitvenih motenj in tudi "oksidacijskega stresa" (prehrana). Različne aberacije kromosomov, ki so zelo značilne za raka prostate (izguba 8p22; amplifikacija 8q24 in X kromosoma), lahko dokažemo že tudi v celicah atrofičnih acinov. Poleg tega je v teh celicah deaktiviran gen (GSTP1), pristojen za tvorbo encimov, ki skrbijo za detoksifikacijo karcinogenov.

**Zaključki.** Molekularna patologija počasi razkriva kavnalne povezave, ki obstajajo med starostjo, arteriosklerozo, prehrano, vnetjem in patogenezo raka na prostati. Mogoče nam bodo v bližnji prihodnosti ta odkritja pomagala v aktivni prevenciji tega najpogostejšega raka starejših moških.

*Ključne besede:* prostata, novotvorba – diagnostika – zdravljenje; patogeneza

## Introduction

The incidence of prostate cancer has increased greatly over recent decades and it is now the most common malignancy of men in many Western countries. The risk of prostate cancer is 1 in 6 and the risk of death due to prostate cancer is 1 in 34<sup>1,2</sup>.

Through PSA (prostate specific antigen) screening the rate of prostate cancers detected at an early stage has increased significantly; thus a decrease in mortality can be expected in the near future<sup>3</sup>. One million prostate biopsies and some 200,000 prostatectomies in Western Europe and the U.S. are the direct consequence of PSA screening. For the same reason, scientific interest in prostate cancer has increased dramatically. The enormous amount of pro-

state tissue available for morphological, biochemical and molecular biological investigations is obviously very helpful for a successful scientific work. Despite all these scientific efforts, however, the molecular mechanisms underlying the development and progression of prostate cancer remain poorly understood.

Prostate cancer is a disease of aging men in Western Europe and the U.S., with the highest rates among Afro-Americans and significantly lower rates among Asiatic men. Epidemiological evidence supports a major contribution through diet, lifestyle and environmental factors to the development of prostate cancer<sup>4</sup>. The level of animal fat intake and consumption of red meat are associated with an increased risk of prostate cancer, whereas vegetables probably protect against cancer<sup>5,6</sup>. The familial predisposition is a risk factor only in < 10% of prostate cancer<sup>7</sup>. There is evidence of both autosomal dominant and X chromosome linked inheritance in some families.

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However, no known cancer syndrome includes prostate cancer.

### Pathogenesis

The cancer forerunner PIN (prostatic intraepithelial neoplasia) is a morphological endpoint of intraglandular cancer development, but it does not explain the pathogenesis of this neoplasm. Recent studies<sup>5,8,9</sup> reappraised the old (1954) hypothesis of Franks,<sup>10</sup> that the atrophy of prostate glands and the subsequent proliferation of the glandular epithelia represent the initial lesion which can develop into cancer.

Atrophy is encountered in more or less all (>90%) prostate biopsies performed for cancer detection and in >80% of autopsy samples.<sup>11,12</sup> This type of atrophy is the focal atrophy which can be classified in 4 subtypes<sup>13</sup> and not the very rare diffuse one, which is due to androgen decrease in circulating blood. But obviously, not all types of focal atrophy can be the starting point for cancer development. Only atrophy with hyperplasia of the basal cells showed a marked proliferative activity of the epithelia and a lower frequency of apoptosis in the atrophic glands.<sup>9</sup> De Marzo proposed the name "proliferative inflammatory atrophy" (PIA) to underline the fact that the lesion is proliferative and associated with inflammation. Inflammation, however, is only one of the common causes of atrophy. But other causes like ischemia or oxidative stress (diet) may be just as frequent as inflammation.

Genetic instability is the basic phenomenon of tissue cell cancerisation. This instability can be hereditary or due to mutations and other chromosomal aberrations acquired during life. Once the genetic material has been disarranged, control and repair mechanisms do not work properly and new injuries lead to further instability.

Chronic inflammation and regeneration is an extremely complex injury which is able to severely disturb genetic programs involved in the control of proliferative activity and apoptosis.

In recent years a large number of interesting data have been collected which show the relationships between prostatitis, subsequent focal atrophy and genetic instability of the prostate epithelia. Even two prostate cancer susceptibility genes are somehow involved in the host response to infectious agents. Mutations can thus reduce the ability to destroy such agents and lead to chronic infection.<sup>4,14</sup> The RNASEL gene, located on chromosome 1q24-25, encodes an endoribonuclease which is involved in the degradation of viral and cellular RNA.<sup>15</sup> Perhaps even more important the macrophage scavenger receptor 1 gene (MSR 1) located at 8p22, which encodes subunits of a macrophage scavenger which is capable of binding ligands including bacterial lipopolysaccharide. Moreover the receptor is involved in the oxidation of high - (HDL) and low - (LDL) density lipoprotein in serum. Mice without MSR gene are vulnerable to many bacterial and viral (Herpes simplex 1) infections.<sup>16</sup> In the prostate this gene is expressed in the macrophages at the site of infection. Mutations in MSR1 were detected in families with hereditary prostate cancer<sup>17</sup> and even in 2.52% of men with sporadic prostate cancer [4]. Loss of chromosome 8p22 seems to be an early event in the prostate cancer progression. Our investigations showed that a significant loss of 8p22 starts already in the epithelia of the atrophic glands in the prostate.<sup>18</sup>

Another important step in the cancerisation is the gain of chromosome 8q24, which could also be demonstrated in the glands of the atrophic areas in the prostate.<sup>18</sup> The gain of 8q24 means amplification of the oncogene *c-myc*, which is involved



**Figure 1.** FISH images of nuclei from prostate cells from atrophic areas. 3 signal for centromere X (Spectrum Orange) and 1 signal for centromere Y (Spectrum Green).

in the immortalisation of prostate cells in cell cultures.<sup>19</sup> In the early stage of prostate cancer *c-myc* probably gives the cells a “proliferative advantage” allowing them to grow under unfavourable conditions. In advanced tumour stages, *c-myc* contributes to the androgen-independent growth of prostate cancer.<sup>20</sup>

Cytogenetical analysis (CGH and FISH) on atrophic areas also detected significant gains of the entire chromosome X (Figure 1) as sole aberration.<sup>21</sup> The androgen receptor gene located on chromosome Xq11-13 encodes the androgen receptor protein through which androgens exert their intracellular regulation of prostate growth and cellular differentiation. Additional androgen receptor gene copies are present in patients with prostate cancer due to polysomy of the chromosome X.<sup>22</sup> Real time PCR demonstrated that even one additional copy of the androgen receptor gene may increase androgen receptor expression suggesting that even small increases in relative gene dosage could have biological significance.<sup>23</sup>

The growth of the prostate cancer is known to be extremely dependent on androgens. Therefore the androgen receptor is an important mediator of androgen dependent cell growth. Examinations of androgen receptor gene alterations in atrophic areas are needed for the early diagnosis of prostate cancer, selection of prevention and treatment strategies. Thus far, it can be assumed that prostate cells with multiple copies of androgen receptor have a selective advantage also in low concentration of androgen.<sup>24</sup> A susceptibility locus on chromosome X, the HPCX (Hereditary Prostate Cancer X) was identified also in prostate cancer families. The X chromosome linked PAGE4 gene is expressed in normal prostate and highly expressed in prostate cancer.<sup>25</sup> Interestingly, a cell line that expresses PAGE4 showed a down-regulation of LPL (lipoprotein lipase), which is located on 8p22 and frequently deleted in prostate cancer and atrophy as already mentioned above.

Another link between inflammation and cancer represents the hypermethylation (inactivation) of GSTP1 gene which encodes a carcinogene-detoxification enzyme. This enzyme defends the prostate epithelia against carcinogens and is present in the basal cells but not in the prostate carcinoma cells.<sup>4</sup> The inactivity of the enzyme leads to damage of the epithelial DNA and to genetic instability.

One of the major objections to this theory is that atrophy of the prostate glands is not always associated with inflammation. Atrophy, however, can also be due to ischemia.<sup>26</sup> In fact, the arteries of the prostate glands show a significantly higher narrowing in patients with prostate cancer than in control groups.<sup>27</sup> The enzyme cyclooxygenase -2 (COX 2) could be a link among different causes, because COX2 is involved in carcinogenesis as well as in inflammation and ischemia.<sup>28</sup> Some studies

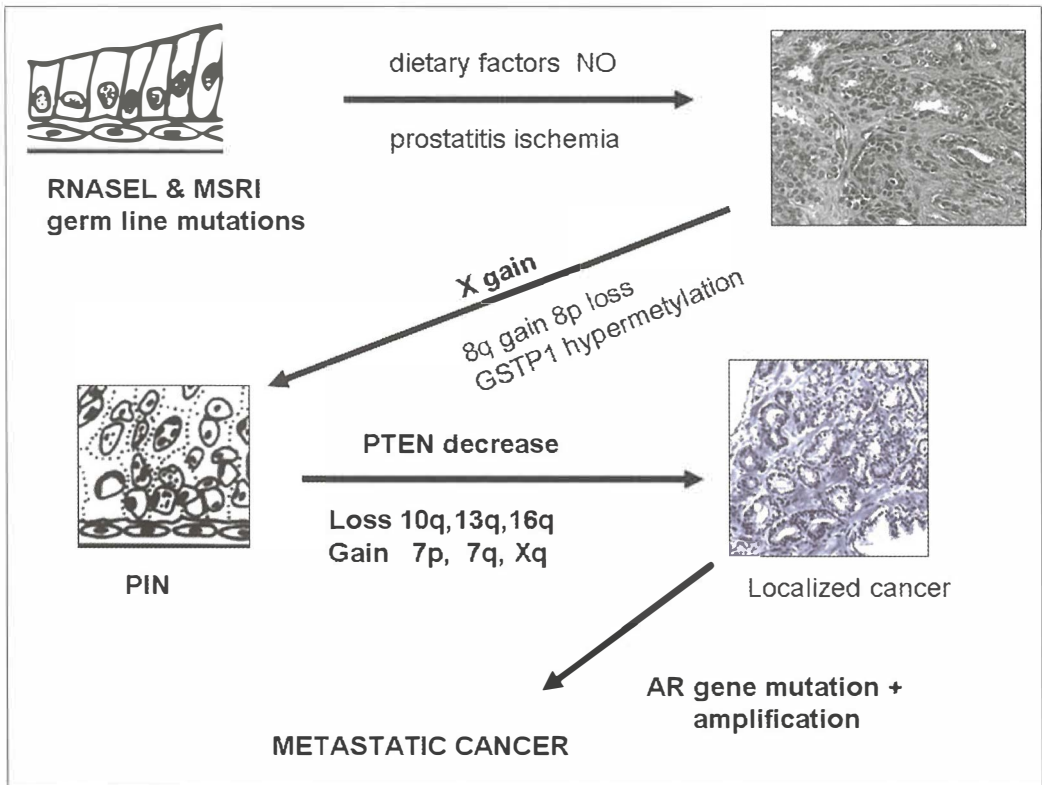


Figure 2. Hypothetical molecular pathogenesis of prostate carcinoma (modified after Nelson).<sup>4</sup>

clearly showed that daily use of non steroidal anti-inflammatory drugs (NSAIDs) significantly reduces the risk of prostate cancer.<sup>29</sup> Moreover, genes (MSR 1) involved in prostate cancer pathogenesis are also involved in lipid metabolism.

### Conclusions

Molecular pathology is slowly revealing the links which exist among age, atherosclerosis and oxidative stress (diet), inflammation and the pathogenesis of prostate cancer (Figure 2). Our knowledge is still fragmentary but we are permitted to hope that in the near future we will be able to actively prevent (NSAIDs, antioxidants?) this most common malignancy of elderly men.

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