前列腺癌靶向基因治疗实验研究的最新进展

Recent advances in experiment and study of prostate cancer targeted therapy

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摘要：近些年，前列腺癌的发病率逐年攀升，针对处于癌症进展期的病人，仍无行之有效的治疗方法。正是由于对这些癌症无计可施，才催生了对更多治疗方法的摸索。经临床研究与实践，基因治疗是目前治疗恶性肿瘤的最有前景的方法。对于前列腺癌，靶向基因治疗是较为理想的治疗方法。然而，现阶段靶向基因治疗的技术并不成熟，缺乏安全、合适的载体便是最为重要的难点。本文就靶向基因治疗的最新成果进行报告，诣在寻找安全可靠的基因载体。

Abstract: In recent years, the incidence of prostatic cancer is on the rise year by year. There is still no effective treatment for progressive cancers. Therefore, more therapies have been investigated for these hard-to-treat cancers. The clinical studies and practice have demonstrated that gene therapy is the most promising method for malignant tumor. For prostatic cancer, targeted therapy is more desirable one. However, the current targeted gene therapies are not mature. The biggest challenge is to find safe and suitable vector. This study reported the most recent results of targeted gene therapy, aiming at identifying safe and reliable gene vector.

关键词：前列腺癌；靶向治疗；基因载体

Keywords: Prostatic cancer; targeted therapy; gene vector

前列腺癌在欧洲属于发病率极高的恶性肿瘤，而在我国虽然发病率并不高，但随着社会的发展、生活水平的提高，前列腺癌的发病率逐年攀升，针对这一发展趋势应给予相应的重视。而且，这一疾病发展至今，曾经有效的治疗方法如传统的放化疗、局限性手术治疗、标准化内分泌治疗均起不到理想的治疗效果。由于缺乏对前列腺癌症行之有效的治疗方法，各国医学家们纷纷探求不同的治疗模式，其中，靶向基因治疗的治疗效果最为可观，既可独立治疗也可联合使用。然而，此项技术尚未成熟，仍有许多难点尚未攻破。缺乏安全有效的载体便是最要紧的一个。

In Europe, prostatic cancer is a malignant tumor with high morbidity. In China, the incidence is not high. With the social development and improved life standard, however, the incidence of prostatic cancer is increasing year by year. More importance should be paid to this trend. The previously effective treatments such as traditional chemotherapy and radiotherapy, limited surgery

and normalized endocrinotherapy fail to achieve good outcomes as the disease develops till this day. Medical scientists are seeking for different treatment patterns since there is currently no effective treatment for prostatic cancer. Targeted gene therapy is the most promising one among them. It can be used alone or combined with other therapies. Unfortunately, this technology is not mature, and many difficulties remain to be addressed. The most urgent one is to find safe and effective vector.

1. 自杀基因治疗

1 Suicide gene therapy

自杀基因治疗是在 1986 年由 Frederid Moolten 首先提出并描述的，是一种效果可观的具有前景的一种治疗手段。[1]自杀基因治疗是利用基因转移技术将自杀基因（即药物酶基因）导入肿瘤细胞中，并将前体药物转化为有毒药物，促使肿瘤细胞凋亡。这种治疗方法可与热、放、化疗联用，提升肿瘤细胞对热、放、化疗的敏感度，从而增强治疗效果。且基因启动子在某些射线下可被激活，产生明显的抑癌效果。这是自杀基因代谢产物的直接毒性作用。

Suicide gene therapy was first described by Frederid Moolten in 1986, which is a promising effective therapy [1]. The suicide gene takes use of the gene transfer technology to transfer the suicide gene (known as drug-modifying enzyme gene) in tumor cells, which translates the prodrug into toxic drug and promotes tumor cell apoptosis. This treatment can be combined with heat therapy, chemotherapy and radiotherapy and make tumor cells more sensitive to these therapies, thereby enhancing therapeutic effects. The gene promoters can be activated by some radiation, and exhibit pronounced tumor inhibition. These are direct toxic effects of metabolites of suicide gene.

此外，“旁观者效应”也是自杀基因治疗的机制之一。在进行自杀基因治疗过程中，人们发现，在肿瘤组织中自杀基因不曾进入的肿瘤细胞活动也受到抑制，即“旁观者效应”。而基因载体系统很难转染入肿瘤细胞，因此，这一机制发挥了重要作用。同时，距离很远的两个肿瘤间也能产生旁观者效应，即为远程旁观者效应。这一发现引发了部分医学家的关注，甚至提出癌症疫苗的思路，但有关这方面，还需要大量的理论研究及临床试验。

Additionally, “bystander effect” is also one mechanism of suicide gene therapy. During the course of suicide gene therapy, researchers found that the activity of those tumor cells in the tumor tissue without exposure t suicide gene is also inhibited, which is the so-called “bystander effect”. This mechanism has an important role in tumor cells where the gene vector system is hard to access. Meanwhile, the bystander effect exists between two tumors far away from each other, also known

as remote bystander effect. This finding attracted attention from some medical scientists. They even proposed vaccine for cancers. However, it remains to be extensively investigated in theoretical studies and clinical trials.

在前列腺癌的治疗中。单纯疱疹病毒-腺苷激酶/更昔洛韦系统是使用最广泛的自杀基因之一，但治疗效果有限。针对这种情况，Chen 等人[2] 建立了一个新的双靶向基因系统，这种靶向系统可以有效地将质粒导入前列腺癌细胞并表达自杀基因。这一系统能抑制癌细胞生长，促使其凋亡。

In the treatments for prostatic cancer, herpesvirus hominis- adenosine kinase/ ganciclovir system is one of the most widely used suicide gene, but the therapeutic effect is limited. In this case, Chen et al [2] established a new double targeted gene system, which effectively transfers the vectors expressing suicide gene to the prostatic cancer cells. This system can inhibit growth of cancer cells and promote their apoptosis.

大肠杆菌嘌呤核苷磷酸/氟达拉滨是最新发现的自杀基因，可被 ARR_2PB 输送。在雄激素类似物 R1881 环境下，被以上基因转染后的前列腺癌细胞对氟达拉滨敏感性得到显著提高，其旁观者效应同样得到提升。

Escherichia Coli purine nucleoside/fludarabine is the newest identified suicide gene, which can be transported by ARR_2PB. Under the environment with androgen analogue known as R1881, the prostatic cancer cells with transfection with the above gene become more sensitive to fludarabine. The bystander effect also enhanced.

分化显示编码 3 是最为典型的前列腺癌指标基因之一，用微小 DD3 启动子联合治疗性 IL-24 增效，形成腺病毒 Ad・DD3-E1A-IL-24，同时具有前列腺特异性与很强的抗肿瘤活性，于是，Ad・DD3-E1A-IL-24 也可作为治疗方法之一。

The differentiation indicates that the code 3 is one of the most typical genetic indicators for prostatic cancer. The tiny DD3 promoter in combination with IL-24 for enhanced treatment forms AD·DD3-E1A-IL-24, which is prostate specific and has strong anti-tumor activity. So AD·DD3-E1A-IL-24 can be used as one therapy.

2. 载体

2 Vector

一个高效安全的靶向基因治疗，很重要的一点就是拥有能成功转运且可以复制表达体内基因的载体。最为理想的状态就是高效率转染、特异性凋亡肿瘤细胞，高效且低副作用。病

毒载体是比较常用的载体，而由于病毒的非特异性感染，导致机体内细胞感染，极易引发严重不良反应，且靶细胞不易被转染，因此其治疗效果不甚理想。

The most important thing of a highly effective and safe targeted gene therapy is to have a vector that can be successfully transported, and replicate and express genes in the body. The most ideal one is to highly transfect the tumor cells and to render specific apoptosis of tumor cells, which is highly effective and causes little side effects. The viral vector is more frequently used one. However, it is easy to cause severe adverse reactions because the infection with virus is non-specific and causes infection of cells in the body. Also, it's not easy to transfect the target cells. Therefore, its therapeutic outcome is not good.

某些非病毒载体也进入人们的视线，以纳米粒子、阳离子脂质体最为常用。Hattori[3]建立了一种新型 NP 载体，经瘤体注射实验表明其具有高效特异性。另外，维生素叶酸也被用作靶向输送。将叶酸与 NP 结合成 NP-F，对鼻咽癌有显著抑制作用。天然高分子载体如壳聚糖，是自然界存在的唯一碱性多糖，安全无毒，有抗菌和直接抑制肿瘤癌细胞的作用，为前列腺癌的靶向治疗提供了新的高效载体的可能性。

Non-viral vectors have also emerged. The nano particles (NPs) and cationic liposomes are most frequently used. Hattori[3]established a new NP vector and demonstrated that it was highly specific in an experiment tumor injection. Natural polymer vectors such as chitosan are the only natural alkaline polysaccharides. It is safe and non-toxic, and has anti-bacterial and direct inhibitory effect on tumor and cancer cells, which provide possibility to be a highly effective vector for targeted therapy of prostatic cancer.

3.联合治疗

3 Combined therapy

3.1.联合病灶局部注射给药

3.1 Combined with local injection

可与病灶局部注射给药，产生协同促进作用，提高对癌细胞的杀伤力。同时避免了放疗，化疗给药带来的副作用。

It can be combined with local injection to produce synergistic effect, which enhances killing effect on cancer cells. It also avoids the toxic effects of radiotherapy and chemotherapy.

3.2.联合免疫治疗

3.2 Combined with immunotherapy

与免疫治疗联合作用，可以通过触发抗肿瘤免疫应答以提升治疗效果。这一点启示我们可用此法激活体内免疫，对抗进展期的前列腺癌。

It can be combined with immunotherapy and enhances therapeutic effect by triggering antitumor immunity. This reveals that this method can activate immunity of the body to fight against progressive prostatic cancer.

3.3.联合抗病毒药物

3.3 Combined with anti-viral drugs

与抗病毒药物联用，能有效降低病毒的不良反应与，减少患者的疼痛，提高患者的舒适度。

It can be combined with anti-viral drug, which effectively reduces adverse reaction of virus, alleviates pains of patients, and makes patients feel more comfortable.

4.小结

4 Conclusion

基因治疗是目前最有前景的治疗前列腺癌的方法，且在此方面获得了不少突破，然而，在技术方面仍然不够成熟，难题依旧存在。仍需要努力寻找毒性小，副作用少的自杀基因；更安全、有效的基因载体，特异性高且高效转染。目前非病毒的天然高分子载体，质脂类，多糖类，多肽类，就提供了更好的研究方向。

Gene therapy is the most promising method for the treatment of prostatic cancer. Many breakthroughs have been made. However, this technology is not mature and a lot of challenges remain to be addressed. Great efforts should be made to find suicide gene with low toxicity and fewer side effects, as well as safer and more effective gene vector with high specificity and effective transfection. Currently, the non-viral natural polymer vectors, lipids, polysaccharides and polypeptides are good candidates to be investigated.

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