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Review

Application of aptamers in treatment and diagnosis of leukemia

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ABSTRACT

Leukemia is a cancer of blood cells and bone marrow, leading to death in many patients mainly in children. Over the last several years, aptamers generated by SELEX (Systematic evolution of ligands by exponential enrichment) method, have quickly become a new class of targeting ligands for drug delivery applications and recently have been widely exploited in different biomedical applications, due to several potent properties such as high binding affinity and selectivity, low or no immunogenicity and toxicity, low cost and thermal stability. In this review, we presented in details about aptamers involved in targeting, and treatment of leukemia. Moreover, some analytical approaches such as electrochemical and optical aptasensors were introduced for detection and diagnosis of leukemia. Finally, we discussed about the directions and challenges of aptamer application in this field.

Contents

1. Introduction

Leukemia is a heterogeneous group of hematopoietic malignancies in which bone marrow produces abnormal white blood cells. Leukemia is classified into two main classes, including Myeloid and Lymphoid, based on the type of the affected white blood cell. There are four main subgroups of leukemia, including

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acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphoblastic leukemia (CLL), and chronic myeloid leukemia (CML). Leukemia results in death in many patients (Ba, 1998; Xie et al., 2003). During the last four decades, great efforts have been devoted to fight against cancer led to the development of new anticancer drugs with higher efficacy and less unspecific effects, as well as improvement of delivery methods such as encapsulation, targeted and controlled release delivery of cytotoxic drugs into the tumor sites (Zhang et al., 2011). Leukemia is still one of the most common lethal cancers (Jemal et al., 2008). Chemotherapy and bone marrow transplantation are the main approaches for leukemia therapy. However, these therapeutic regimens for leukemia show a rather narrow spectrum as compared with those are available for solid tumors. In solid tumors, cancerous cells accumulate at tumor sites, so the anticancer drugs could have access to tumor sites through enhanced permeation and retention (EPR) effect, while this condition does not exist for leukemia, as leukemia cells are prevalent in the whole circulatory system. On the other hand, leukemia cells are surrounded by normal blood cells. So that, normal blood cells could also be affected with toxic agents. Therefore, a targeted and potent approach for treatment of leukemia cells which could specifically kill leukemia cells without affecting normal blood cells, would be extremely desirable (Barth et al., 2011; Chari, 2007).

Aptamers are artificial short single-stranded oligonucleotides, selected and generated through an in vitro molecular method called SELEX (Systematic evolution of ligands by exponential enrichment). Sizes of aptamers differ from 20 to 80 nucleotides. They have high binding affinity and specificity towards a wide range of targets, including small ions, phospholipids, antibiotics, virus, proteins, toxins and even entire cells and tissues. In comparison with traditional antibodies, aptamers are nontoxic, very stable at a vast range of pH, temperature and ionic environment and can be easily modified with various tags and possess lower immunogenicity and long half-life (Citartan et al., 2012; Danesh et al., 2016; Emrani et al., 2016; Song et al., 2012). Moreover, aptamers contain smaller size compared to antibodies, leading to faster and more internalization of aptamers into tumors. Due to these excellent properties, applications of aptamers are growing quickly in the both treatment and diagnosis of cancers (Liu et al., 2013). Here, we summarized the recent progress of aptamer applications in the diagnosis and treatment of Leukemia. Finally, we discussed the problems and future perspectives in their diagnostic and therapeutic applications.

2. Applications of aptamers in leukemia diagnosis

2.1. SELEX approach for diagnosis of leukemia biomarkers

Based on the sample used in SELEX method for recovery of aptamer from the initial library (Fig. 1), SELEX approach is divided into two main classes, including Protein-SELEX and Cell- SELEX. In Protein-SELEX, starting from purified or recombinant proteins as target for SELEX, the control of SELEX condition is easier to achieve optimal enrichment during the selection procedure compared to Cell-SELEX. However in Cell-SELEX, using the whole cell as target, aptamers are generated for the native conformation and exposed parts of targets on the surface of cancer cells, leading to better access and internalization of aptamer to cancer cells. Furthermore, Cell-SELEX is favored when there is no prior knowledge for specific marker on the cell surface (Guo et al., 2008; Ohuchi, 2012).

Based on Cell-SELEX approach, Shuangguan and coworkers developed a panel of aptamers, called sgc aptamers, for the specific recognition of leukemia cell (CCRF-CEM, T-cell lines, human acute lymphoblastic leukemia) in the presence of normal human bone

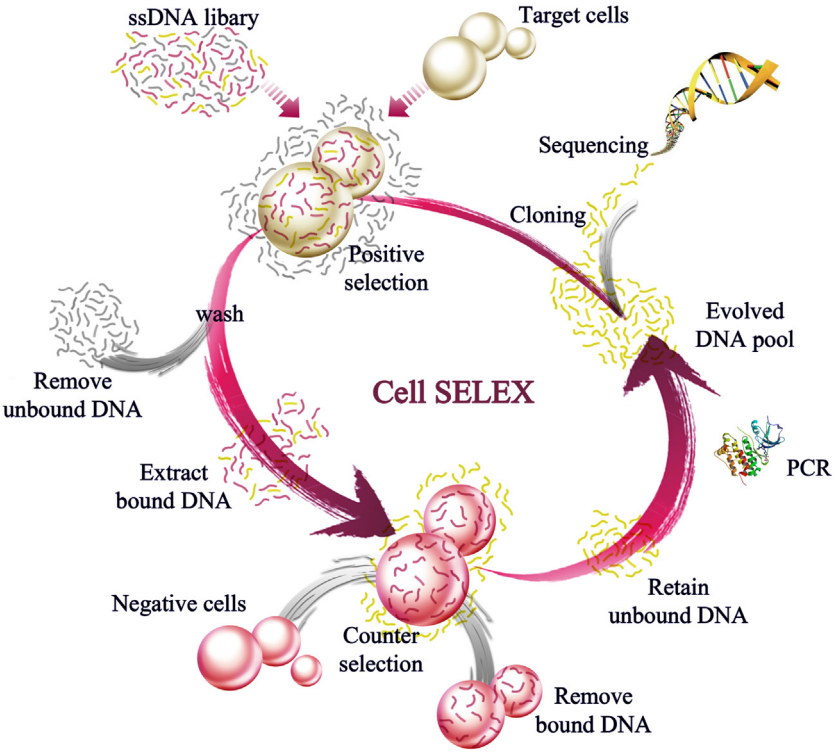

Fig. 1. Schematic depiction of the cell- SELEX. During this process, a single-stranded nucleic acid library was first incubated with target cells (CCRF-CEM cells). Following washing, the bound DNAs were eluted by heating to 95 °C. For counter selection, the eluted DNAs were then incubated with Ramos cells (negative cells). Then, the unbound DNAs were eluted and amplified by PCR. The PCR products were separated into ssDNA to start next-round of selection. This process continue until a DNA pool with high affinity and good selectivity for the target cells was achieved. Adapted from the published work (Shangguan et al., 2006).