Profiling Cancer Cells by Cell-SELEX

Subjects: Cell Biology

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The identification of tumor cell-specific surface markers is a key step towards personalized cancer medicine, allowing early assessment and accurate diagnosis, and development of efficacious targeted therapies. What mainly limits the number of ideal clinical biomarkers is the high complexity and heterogeneity of several human cancers and still-limited methods for molecular profiling of specific cancer types. The cell-SELEX (Systematic Evolution of Ligands by Exponential Enrichment) technology for the differential selection of oligonucleotide aptamers against a specific cancer-cell type has become the selection technique for the discovery of cell-surface markers. Indeed, it allows selection, at the same time, of a set of aptamers acting as highly efficacious recognition elements for functional surface signatures of target cells. Importantly, these aptamers may be used to identify cell-surface molecules whose role is still unexplored. This fulfills the great challenge of simultaneously targeting multiple proteins whose alterations, in concert, define the pathological state of the cell and are thus more informative for biomarker discovery than the alteration of a single protein.

cell-SELEX aptamer cancer cell phenotype biomarker discovery cell-profiling targeted therapy

1. Profiling Cancer Cells by Cell-SELEX

One of the greatest advantages of cell-SELEX is the possibility to perform the selection against a specific cell type without the prior knowledge of protein targets present on its surface. In such a way, a panel of aptamers can be generated that specifically recognizes the surface signature of the target cells and, through it, can distinguish those cells from the cells chosen for the counter-selection. These aptamers are applied as useful bioreagents for active cancer targeting and, notably, can be used as bait for the identification of new protein targets, playing an important role in biomarker discovery (**Figure 1**).

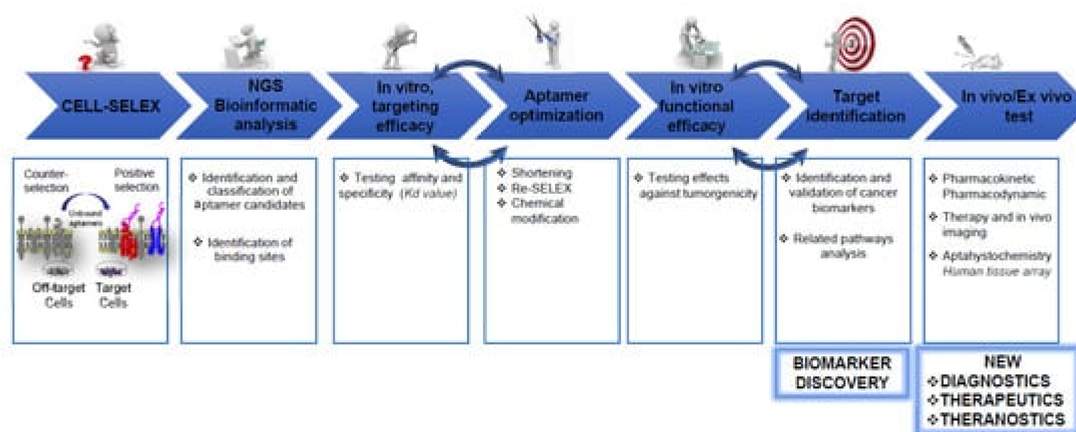

Figure 1. Aptamer discovery and development process. The image shows the sequential steps from the generation of aptamers by SELEX to their preclinical development as cancer-targeted therapeutics, imaging agents for diagnostics and theranostic molecules. Briefly, cancer cell-specific aptamers are generated by cell-SELEX against a specific cell type, without the prior knowledge of the molecular target. High affinity ligands are identified by classical cloning and/or high-throughput sequencing and bioinformatic analysis. The best aptamer candidates are tested in vitro for their affinity and specificity, optimized to increase their binding efficacy and tested in vitro/in vivo as cancer-targeted agents. The best binding aptamers are used as bait to identify their cell-surface targets, thus leading to discovery of novel biomarkers.

Cell-SELEX has been applied to different tumor types, including highly aggressive and heterogeneous cancers that lack well-defined biomarkers for a targeted therapy, with the intent to discover new aptamers able to bind to surface proteins, which differ in expression level between healthy and unhealthy cells or among different cancer cell phenotypes.

The first group who realized the opportunity to dissect biological complex targets using SELEX technology was Morris and Jensen's group in 1998. They used human red blood cell membrane preparations as a complex mixture of potential targets to select a set of cell-specific ssDNA aptamers with high affinity for different cell membrane proteins[1].t was not long before there was an understanding that this approach could be also applied to decode the specific surface signature of different kinds of cancer cells.

Tan's group applied the SELEX technology to living cells to explore membrane protein biomarkers. In their pioneering work, they screened a DNA library on cultured precursor T cell acute lymphoblastic leukemia (ALL) to generate a panel of aptamers specifically discriminating target cells from human Burkitt's lymphoma cells, used in the counter-selection steps. In particular, five aptamers (sgc8, sgc3, sgd3, sgc4, and sgd2) were able to bind to target cells at high affinity, with K_D values ranging from 0.80 ± 0.09 nM (sgc8) to 26.6 ± 2.1 nM (sgc4), and other ALL cell lines, but not to cultured B cells and acute myeloid leukemia (AML) cells [2]. In addition, these aptamers could discriminate different leukemia cells (T-ALL, B-ALL, AML) in clinical samples, thus detecting subtle molecular differences among individual samples from leukemia patients in the same category [3]. Post-SELEX target identification, based on aptamer-mediated affinity purification and mass spectrometry, allowed the match of sgc8 aptamer with its target, the transmembrane receptor protein tyrosine kinase 7 (PTK7) [4]. Subsequently, as

discussed below, this aptamer was applied as a new therapeutic tool for haemato-oncological malignancies [5]. By using a similar strategy, Tan's group also identified the immunoglobin heavy mu chain as the target for TD05 aptamer, which was selected by using the Burkitt's lymphoma cell line Ramos as the target [6]. Both of these studies demonstrate that this two-step strategy, the development of high-quality aptamer probes and the identification of their target proteins, is a powerful approach for biomarker discovery.

Through the use of several protocols, essentially based on altering positive selection steps on the chosen target cells and counter-selection steps on off-target cells, several aptamers have been to date developed with binding to unknown but unique characteristic surface proteins of target cells. For instance, aptamers have been generated that are able to discriminate high-metastatic from low-metastatic cancer cells of different tumor types, including colorectal carcinoma [7], breast cancer [8][9][10], osteosarcoma [11], prostate cancer [12][13] hepatocellular carcinoma [14][15][16] and colon cancer [17][18]. The generation of the above aptamer probes specifically targeting metastatic cancer cells provides a significant tool for diagnosis and treatment of the metastatic disease. For one of them, the investigation has already progressed to the target identification. Indeed, the RNA Apt63 aptamer, generated by a cell-SELEX approach for differential binding to prostate cancer cell lines with high vs. low metastatic potential, when used for aptamer-based affinity purification combined with mass spectrometry, matched to the plasma membrane ATP synthase beta subunit (ecto-ATP5B). Testing of the aptamer in vitro, as well as in xenograft models and human samples, proved this protein is a new marker for predicting and treating metastatic breast and prostate cancers [13]. Moreover, applied to cancer cells belonging to different tumor types (pancreatic cancer PANC-1 cells vs. hepatocarcinoma Huh7 cells) a blind cell-SELEX approach raised an aptamer able to regulate epithelial–mesenchymal transition (EMT) and inhibit metastasis in pancreatic cancer by binding to cell-surface vimentin, as revealed by post-SELEX liquid chromatography tandem mass spectrometry analyses [19].

It is known that cancer stem cells (CSCs) represent a small fraction of cells within a tumor mass exhibiting self-renewal and tumor-initiating capabilities, which contribute to recurrence, metastasis and therapeutic resistance. Unfortunately, specific biomarkers for CSCs are lacking, thus it remains extremely hard to eradicate them by effective therapeutic strategies [20]. Notably, differential cell-SELEX has been applied to identify new markers of CSCs. Some groups succeeded in generating aptamers able to differentiate glioma stem cells from differentiated cells [21][22], highlighting the potential of aptamers to target a molecular signature of CSCs for therapeutic applications. Similarly, aptamers have been generated to bind stemness-enriched cells in colorectal [23], pancreatic [24] and prostate [25] cancers. The identification of the molecular targets of these aptamers may reveal new CSC biomarkers.

Further, to address the issue of resistance to therapy, cell-SELEX has been applied to discriminate drug-resistant cancer cells from sensitive counterparts. Recently, by using vemurafenib-resistant melanoma cells as a target of the selection and sensitive cells in counter-selection steps, Li et al. identified an aptamer specifically binding to CD63 on the surface of cancer cells [26], thus opening the possibility to interfere with the TIMP-1/CD63 interaction at the cell surface, which recently emerged as a driver of malignant progression in melanoma and other human cancers [27]. Furthermore, by a SELEX approach using taxol-resistant colon cancer cells in the positive selection and parental cells in counter-selection steps, Zhang et al. identified a DNA aptamer binding to human TfR at affinity

comparable to that of human Tf. Importantly, they proved the ability of the aptamer to cross the intestinal epithelium barrier through TfR-mediated transcytosis, indicating its potential as a carrier for active drug delivery [28].

In addition, we applied the differential cell-SELEX approach to different tumors, including NSCLC [29] and glioblastoma (GBM) [30], to generate aptamers able to target, within the same tumor type, cells characterized by a phenotype more aggressive than that of the cells used in the counter-selection, in terms of resistance to chemotherapy and tumorigenicity. Combining different post-SELEX biochemical approaches, we were able to identify EGFR and platelet-derived growth factor receptor beta (PDGFRβ) as the molecular targets of CL4 and Gint4.T aptamers, respectively, with the first coming from the selection on NSCLC cells [29] and the second from that on GBM cells [30]. Both 2′-fluoro-pyrimidine (2′-F-Py) containing RNA aptamers were subsequently validated as ligands and inhibitors of their proper receptor targets, not only when applied to cancer cells used for their selection but also in different tumor types, thus contributing to insight on the oncogenic role of these two RTKs, depending on the specific tumor expressing them. For instance, the anti-EGFR CL4 aptamer exerts a strong apoptotic effect on human NSCLC [29], blocks the invasiveness of GBM cells expressing either the EGFRwt or EGFRvIII mutant [30][31] and prevents the EGFR/integrin αvβ3 interaction on the surface of TNBC cells with a mesenchymal stem-like phenotype, which we first found to be required for vasculogenic mimicry and tumor growth of aggressive and poorly differentiated TNBC subtype [32][33].

Similarly, the Gint4.T aptamer acts as a neutralizing ligand for PDGFRβ in cell lines, primary cultures and xenografts models of GBM [30]. Further, it has been applied as a highly effective tool for imaging and suppression of TNBC lung metastases, thus indicating PDGFRβ as a reliable biomarker of a subgroup of TNBCs with invasive and stemlike phenotype [33][34]. More recently, Gint4.T has been proven to potentiate the efficacy of immunotherapy with anti-programmed death-ligand 1 (PD-L1) mAb in the inhibition of tumor growth and metastasis in a syngeneic TNBC mouse model [35].

Moreover, several cell-SELEX protocols have been applied to cancer cell lines by using normal cells for the counter-selection with the aim to identify novel cancer biomarkers for improving early diagnosis and therapy. For instance, 2′-F-Py RNA aptamers were selected on two different pancreatic cancer cell lines able to bind target cells and discriminate them from normal pancreatic ductal cells. Interestingly, aptamer-based target pull-down experiments on cell membrane lysates, combined with a genome-wide microarray analysis in cells targeted or not by the aptamer, identified the oncofetal protein alkaline phosphatase placental-like 2 (ALPPL-2) as the target of one of the selected aptamers and attributed a novel function to this protein as promoter of pancreatic cancer cell growth and invasion [36]. By a similar approach, four aptamers were identified that differentiate nasopharyngeal cancer cells from nonmalignant nasopharyngeal cells, the cell-surface receptor CD109 identified as the target of one of them [37]. The overexpression of CD109 in many human cancers and its association with metastasis and chemoresistance makes it an attractive target for diagnosis and therapy [38].

Moreover, in order to generate aptamers against tumor cells in more physiologically conditions, 3D cell-SELEX protocols have been applied to spheroids of prostate [39] and breast [40] cancer cells by using nontumor cells for the negative selection.

2. Unravel Cancer Heterogenicity by Cell-SELEX

One of the major factors limiting the number of effective targeted therapies is represented by cancer heterogeneity. Indeed, cancer is a dynamic disease and various cell subpopulations develop during its course, which are characterized by unique genotypes and phenotypes correlating to different biological behaviors and sensitivity to treatments. Distinct molecular signatures can be found among different tumors or inside the same one (inter- and intratumor, respectively). At the basis of the intratumor heterogeneity, there is a continuous process of evolution that involves all tumor cells, not only in time but also in space. For instance, Zhao et al. observed that the location of genetically distinct subclones in a tumor reveals their evolution, with the most aggressive and prone to metastasis located in the center of the tumor [41].

Phenotypic heterogeneity in different cell populations contributes to cancer drug resistance and hampers treatment outcome [42], but sufficient characteristics have not yet been determined to allow discrimination of the subpopulations present in a tumor. Cell-SELEX is an important approach for unraveling differently expressed cell-surface proteins of heterogeneous cancers such as GBM, breast and pancreatic cancers, which still lack personalized treatment protocols.

2.1. GBM

GBMs, classified as grade 4 astrocytomas, are the most frequent and aggressive malignant tumors occurring in the human brain and, according to gene expression, they were classified by the TCGA consortium into four molecular subtypes (proneural, mesenchymal, neuronal and classical) associated with different prognosis [43]. One of the main reasons for GBM aggressiveness is its intrinsic intratumor heterogeneity; indeed, it is composed of tumor stem cells, differentiated tumor cells, cells from the blood vessels, and inflammatory cells. The existence of these different subpopulations and their interactions with the TME components contributes to resistance to conventional treatments [44].

In order to create new opportunities for better treatment options, Lin et al. [45] applied a cell-SELEX protocol to human glioma SHG44 cells, a grade 3 human anaplastic astrocytoma, by using human astrocyte SVGp12 cells, for counter-selection. Aptamer S6-1b, obtained by truncating the long version coming from the selection, showed excellent specificity, discriminating target cells from SVGp12 cells and other cancer cell lines, including GBM U87, T98G and U251 cells. Cy5-labeled aptamers, intravenously injected in mice bearing subcutaneous SHG44-derived tumors, rapidly accumulated in the tumor and persisted for over 4 h, resulting in useful tools for noninvasive imaging of the tumor. Aptamer-mediated affinity purification of cell membrane proteins identified fibronectin, an extracellular matrix protein overexpressed in glioma, as the potential target of S6-1b.

Further, using SELEX technology on T98G target cells and SVGp12 off-target cells, Wu et al. selected two aptamers, WYZ-41a and WYZ-50a, able to bind to T98G but not to either U87 and U251 GBM cell lines [46] consistently, with major differences at the cell surface among them [47]. The aptamers were stable for 2 h and

retained their binding capability in cerebral spinal fluid, thus indicating a great potential in using these aptamers for biomedical applications.

In addition, among a group of DNA aptamers selected on a cell line (K308) derived from gliosarcoma, a variant of GBM, WQY-9 aptamer was capable of recognizing gliosarcoma cells and gliosarcoma tissues, differentiating gliosarcoma from GBM [48].

2.2. Breast Cancer

Luminal A, Luminal B, HER-2 enriched and TNBC represent the four main subtypes of breast cancer [49]. They are characterized by different behavior and therapeutic sensitivity. Hence, dissecting the heterogeneity of its subpopulations is also necessary for the management of breast cancer. A differential cell-SELEX was applied to HER2-overexpressing breast cancer SK-BR-3 cells by using a pool of three counter-selections against Luminal A MCF-7 cells, breast normal MCF-10A cells and TNBC MDA-MB-231 cells. The length-optimized sk6Ea aptamer, resulting in the best binding candidate, was able to bind specifically to the target cells without recognizing the three counter-selection cell lines both in vitro and in vivo, upon intravenous injection in subcutaneous tumor-bearing mice. Moreover, sk6Ea when cemented on breast cancer tissue sections, efficiently discriminated the three different breast cancer subtypes [50].

TNBC, defined by the lack of ER, progesterone receptor (PR), HER-2 expression, is significantly more aggressive than other breast cancers, diagnosed at a later stage and more likely to develop recurrence. It is highly heterogeneous and the presence of different subtypes, related to different cancer features, makes it difficult to establish an appropriate therapy [49]. Lehman et al. classified TNBC into four subtypes: Basal-like 1, Basal-like 2, mesenchymal and luminal androgen receptor [51][52]. Recently, we applied a cell-SELEX method for the specific recognition of MDA-MB-231 cells, a highly metastatic human cell line representing an established model for the aggressive and undifferentiated mesenchymal TNBC subtype [53]. At each round, the positive selection step on TNBC cells was preceded by counter-selection against non-TNBC breast cancer BT-474 cells, which express high level of ER, PR, and HER-2, and A431 epidermoid cancer cells. By using high-throughput NGS and bioinformatics, we identified a panel of six 2′-F-Py RNA aptamers able to bind to human TNBC cell lines (MDA-MB-231, BT-549, MDA-MB-436, DU4475, MDA-MB-468) covering different TNBC subtypes, and to distinguish them from both normal cells and non-TNBC breast cancer cell lines representative of luminal A (MCF-7 and T47D) and HER2-positive (SK-BR-3) molecular categories. Further, these aptamers can be used for staining of histological tissues to differentiate TNBC human samples, showing a distinct pattern of binding on different tumors [53]. In addition to their binding capability, the aptamers actively internalize into target cells and inhibit the mammosphere-forming ability of TNBC cell lines. Therefore, we anticipate that the identification of their targets will help to expand the limited repertoire of actionable TNBC biomarkers.

2.3. Pancreatic Cancer

Pancreatic cancer is classified as basal, with the worst prognosis and classical clinical subtypes. More than 70% of patients are unresponsive to the current therapies, and despite many efforts made in past years there are no

improvements, principally due to its great heterogeneity [54]. To determine if there were molecular markers differently expressed on pancreatic cancer, Yoon et al. investigated the expression of seven different markers (five EMT markers, one proliferation marker, and one leukocyte antigen marker) on human cancer tissues by using a multiplexed tissue imaging mass cytometer platform. They observed a substantial heterogeneity both intratumor and in tumors of the same grade [55]. Nevertheless, a cell-SELEX protocol using pancreatic cancer PANC-1 cells for the positive selection and hepatocellular carcinoma cells for counter-selection led to the identification of mitochondrial heat shock protein 70 or mortalin, as a potential biomarker of pancreatic cancer [56]. This protein is expressed on the surface of cells belonging to some human cancers, such as colorectal, neuronal and pancreatic, but not to normal tissues.

2.4. TME

The role of stroma microenvironment in both solid tumors as well as malignant haematological disease is well-accepted. Based on the high level of heterogeneity in the nature of mutations present between patients and even within patients during the different stages of their disease as well as the clear role of tumor/stroma interactions in chemoresistance, targeting interactions between tumor cells and their stroma provide new therapeutic approaches [57]. Because of the role of tumor-associated macrophages (TAMs) in supporting tumor progression and dissemination and their linking with worse clinical outcome and resistance to conventional therapies, many efforts are focused on the development of TAMs-targeted strategies for cancer treatment. To this aim, Sylvestre et al. aimed to identify by cell-SELEX an aptamer able to target this cell population, discriminating it from resident (M0-like) or tumoricidal (M1-like) macrophages [58]. Despite the use of negative selection screens on monocytes and M0-like macrophages, and positive selection on M2-like macrophages, resembling TAMs, they selected an aptamer, named A2, that binds to both human M0- and M2-like macrophages and monocytes, probably due to overlapping receptor expression between M0- and M2-like macrophages. Conversely, A2 does not recognize M1-like macrophages or other leukocyte populations. Because of its binding and internalization into CD14+ but not CD16+ monocytes, which is also observed in vivo, A2 holds great potential for drug delivery approaches targeting monocytes. Based on the binding behavior of A2 to monocytes, they hypothesized and then confirmed that the aptamer binds to the CD14 receptor, which is expressed by both monocytes and macrophages.

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