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Review Article

Basic approaches, challenges and opportunities for the discovery of small molecule anti-tumor drugs

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Abstract: Chemotherapy is one of the main treatments for cancer, especially for advanced cancer patients. In the past decade, significant progress has been made with the research into the molecular mechanisms of cancer cells and the precision medicine. The treatment on cancer patients has gradually changed from cytotoxic chemotherapy to precise treatment strategy. Research into anticancer drugs has also changed from killing effects on all cells to targeting drugs for target genes. Besides, researchers have developed the understanding of the abnormal physiological function, related genomics, epigenetics, and proteomics of cancer cells with cancer genome sequencing, epigenetic research, and proteomic research. These technologies and related research have accelerated the development of related cancer drugs. In this review, we summarize the research progress of anticancer drugs, the current challenges, and future opportunities.

Keywords: Drug therapy, cancer, inhibitor, comprehensive utilization

In the 1940s, nitrogen mustard was found to cure malignant lymphoma in humans [1] which has boosted researchers' confidence in curing cancer. With the rapid development of biology, people have researched the subjects including biochemistry, immunology, and therapeutics [2-4], leading the cognition of tumors to a genetic level [5-7]. The clinical application of various antitumor drugs has continually prompted researchers to explore many new antitumor drugs [8-10].

Small molecule drugs mainly refer to chemical synthetic drugs with molecular weight less than 1000, of which structure has good spatial dispersion and leads to their high drug efficiency and pharmacokinetic properties [11]. As a result, the market started to focus on those drugs. Small molecule anticancer drugs, usually signal transduction inhibitors, can block the signal transduction pathways for tumor growth and proliferation, then to cure the tumor [12] such as, Novartis Gleevec's for the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors and AstraZeneca's treatment of non-small cell lung cancer with epidermal growth factor receptor (EGFR) as the target. Small molecule drugs have already had the advantages of wide use and mature theory.

Although small molecule drugs have achieved encouraging results, there are still many challenges. Disobedience of the rational drug use would increase the side effects and drug tolerance, leading to poor treatment effect [13]. Secondly, small molecule drug monotherapy, especially protease inhibitors, cancer cells are prone to cause drug-resistant mutations in about 2 weeks [14]. In addition, small molecule drugs are prone to generate multi drug resistance sites. In a word, the small molecule drugs are in the ascendant, and new drugs are constantly emerging, which has made the anti-cancer and anti-tumor drug treatment essential [15]. With the continuous development of such drugs with low drug resistance, high efficacy

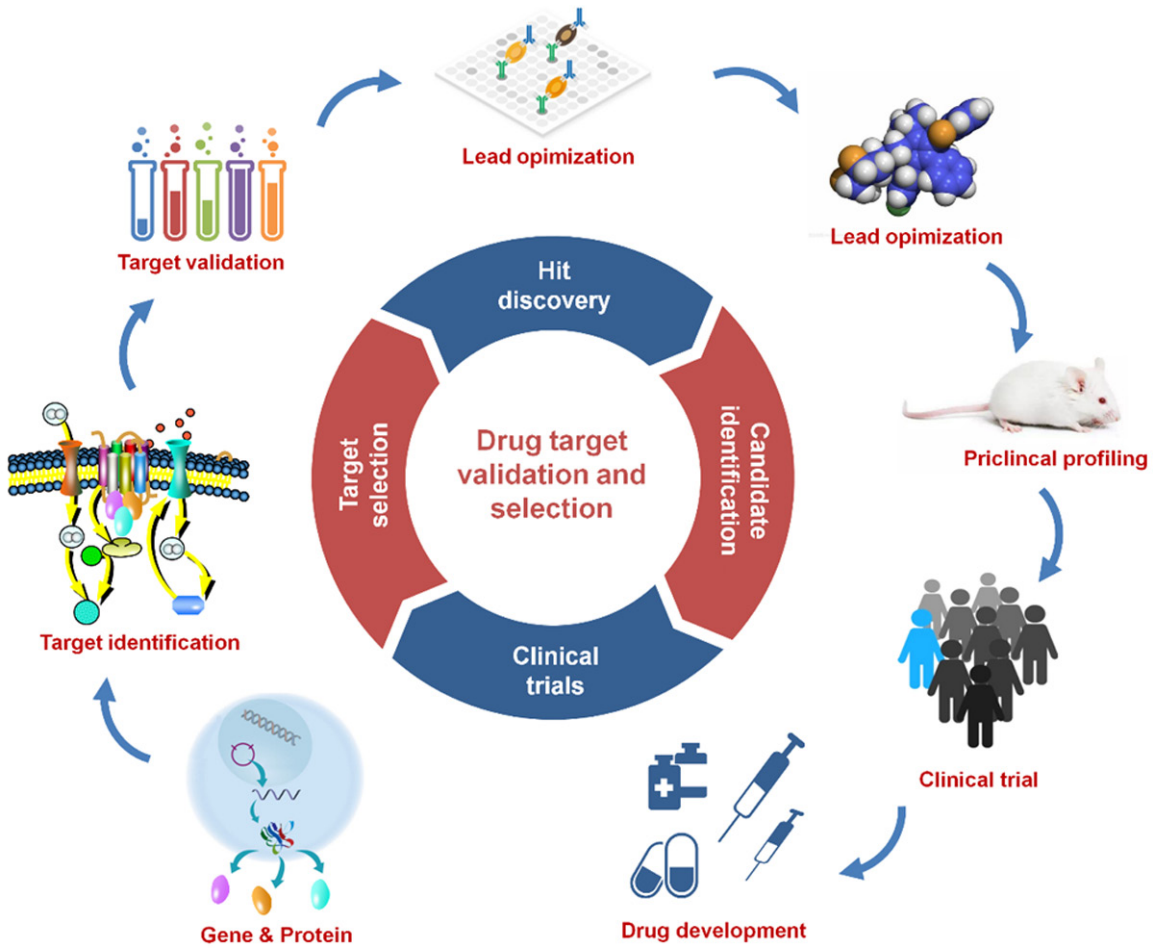

Figure 1. Discovery and development from gene to drug. Small molecules that act on new molecular targets represent therapeutic dependencies and vulnerabilities. There are four main steps of cancer drug discovery: target selection and validation, chemical hit and lead generation, lead optimization to select a clinical candidate, and biology-led clinical trials.

and few side effects, it is believed that in the near future, there will be significance breakthrough in the treatment of cancer.

Nowadays, novel and effective antitumor drugs is urgently needed. The basic approaches, challenges, and opportunities for the discovery of antineoplastic agents are summarized below.

Drug target selection

Choosing the right target needs to balance benefits and risks, which is one of the most critical problems [19-21]. Wrong drug target is a costly waste of drug research and development [22-24]. In general, the selection of targets depends on a detailed understanding of the molecular mechanism (**Figure 1**). After the target activity is regulated in pharmacology (including activation or inhibition), it can achieve antitumor effects both *in vitro* cell system and *in vivo*, and has selectivity for cancer cells with few side effects [25-27].

Naturally-derived drugs

Naturally-derived drugs kill tumor cells by inhibiting proliferation and inducing apoptosis aiming at metabolic heterogeneity; the drugs also act on tumor cells in indirect manners, such as immune regulation and epithelial-mesenchymal transition (EMT) inhibition of metastasis (**Figure 2**). Therefore, researchers have focused on identifying natural products to use as drugs for treating cancer [29].

At present, more than 2,000 plants have been screened for anticancer activity in China, 190

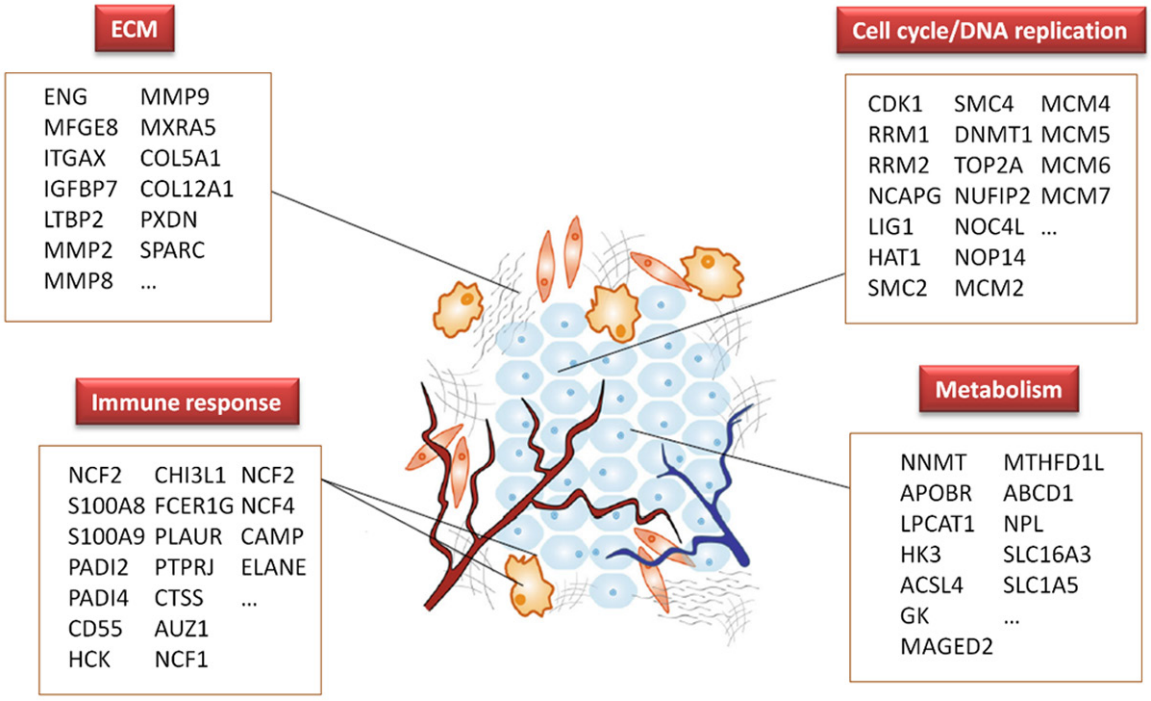

Figure 2. Potential drug targets for targeted therapy. Common proteins upregulated in the majority of tumors were classified in the four functional categories: proteins involved in extracellular matrix (ECM), immune response, cell cycle/DNA replication, and metabolism.

have shown anticancer activity in animal experiments [30]. Paclitaxel is an alkaloid compound isolated and purified from the bark of the gymnosperm yew [31]. When treated with paclitaxel, the cells would accumulate microtubules interfere with various functions of the cells, such as blocking the normal cell division [32]. In Phase II-III clinical studies, paclitaxel is mainly used for ovarian cancer [33] and breast cancer [34]; it has also shown to have some beneficial effects against lung cancer, colorectal cancer and melanoma [35-38]. Another plant called vinorelbine is a cell cycle-specific drug with semi-synthetic compound [39]; the plant navelbine could stop mitosis in the metaphase by blocking tubulin polymerization to form microtubules and induce tubule formation disorders [40, 41].

Synthetic antitumor drugs

Chemical antitumor drug refers to cytotoxic drug and acts on the chemical structure of DNA [42], which plays an irreplaceable role in treating cancer; These drugs are mainly alkylating agents, antimetabolites, antitumor antibiotics, platinum complexes, and targeted drugs [43]. However, while these drugs kill cancer cells, normal cells would also receive detrimental effects [45]. Besides, the significant drug resistance and allergic reactions have also limited their long-term clinical applications [46-48]. Therefore, chemical antitumor drugs with low toxicity and high efficiency are an urgent issue for pharmaceutical companies.

Alkylating agents were one of the earliest classes of drugs for cancer treatment are mainly used for chronic lymphocytic leukemia and malignant lymphoma [49], which could generate a carbocation or other compound with an electrophilic group *in vivo* [50]. These reactive electrophilic species can covalently combine with electron-rich groups (e.g., amino, sulfhydryl, hydroxyl, carboxyl, and phosphate) in biological macromolecules (e.g., DNA, RNA, and enzymes) in cells [51-53]. This combination would cause loss of biological macromolecule activity or cleavage of DNA molecules, resulting in death of tumor cell and antitumor activity [54-58].

Antimetabolites are a class of drugs that affect the biosynthesis of nucleic acids [59], which

chemical structure is similar to what nucleic acid metabolism required. Antimetabolitescan prevent cell division and proliferation by specifically interfering with the metabolism of nucleic acids including methotrexate, 6-mercaptopurine, 5-fluorouracil (5-FU), and cytarabine [60, 61]. Deoxyfluorouridine is a prodrug of 5-FU [62], which could be decomposed into 5-FU by pyrimidine nucleoside phosphorylase after entering the body in order to kill the tumor; it is used clinically to treat breast and digestive tract tumors clinical [63]. Is a congener of cytarabine [64], its one nucleotide can allow intrusion, and the second nucleotide can inhibit the multimerization process after breaking DNA, forming a mask chain break [65]. Difluoro deoxy cytarabinealso inhibits nucleotide reductase and inhibits DNA synthesis, which means it is one of the first choices in treating non-small cell lung cancer (NSCLC) and pancreatic tumors [66]. Antitumor antibiotics, containing dimethoxy daunorubicin, which has high fat solubility and a strong anti-leukemia effect, are extracted from a class of microbial culture fluids that interfere with transcription by directly disrupting DNA or embedding DNA [67]. Puromycinis a semi-synthetic antibiotic with a tetrahydropyran at the 4-position of doxorubicin [68] which can inhibit DNA replication and transcription, and block the cell cycle in the G2 phase; it has a wide antitumor spectrum and can inhibit tumor metastasis [69]. The cardiotoxicity of puromycin is no higher than epirubicin, it's side effect of hair loss is significantly lower than other anthracyclines during the clinical treatment of breast cancer and lymphoma [70].

The anticancer mechanism of platinum antitumor drugs can be divided into four steps: transmembrane transport, hydration dissociation, targeted migration, and action on DNA, which may cause DNA replication disorders, thereby inhibiting the division of cancer cells [71-73]. Preclinical studies have shown significant inhibitory effects on colorectal tumor cell lines and cisplatin-resistant cell lines, and significant synergistic effects with 5-FU [74-76]. Nidaplatin is more effective than isodose cisplatin in the head and neck, testis, lung, esophagus, bladder, ovary, and cervical tumors, while digestive tract reaction and nephrotoxicity are mild [77-79].

Molecularly targeted drugs are often targeted at key enzymes in cell signaling pathways involved in tumor cell differentiation and proliferation, also screen for low-toxic, highly potent, and specific small molecule compounds that selectively act on specific targets [80-82]. It was first used clinically in an antitumor small molecule compound with a single kinase target, which easily produces drug resistance with a narrow therapeutic range [83]. Most solid tumors are multi-link and multi-target. Multinomial integration analysis that are essential tools for stratifying patients according to risk factors provide insights to use more targeted and individualized therapeutics (**Figure 3**). Blocking a certain target or receptor does not need to block the signal transduction of all cells, so multi-kinase targeting represent a new development direction of tumor-targeted therapeutic [84], including targeted drugs that inhibit tumor angiogenesis, protein tyrosine kinase inhibitors, and mammalian target of rapamycin (mTOR) inhibitors [85].

Targeted drugs that inhibit tumor angiogenesis include inhibit vascular endothelial growth factor (VEGF) such as bevacizumab for the treatment of NSCLC, panitumumab, cetuximab, trastuzumab, and some other drugs [86-88]. There are also targeted drugs inhibit angiogenesis directly such as endostatin and angiostatin, the two endogenous tumor neovascular inhibitors that inhibit tumor angiogenesis, induce tumor cell apoptosis, prevent tumor invasion and metastasis by inhibiting the growth of tumor endothelial cells [89]. Both drugs inhibit angiogenesis directly, being used in clinical practice in China [90].

Sorafenib is a multi-target inhibitor inhibit targets for Fms-like tyrosine kinase, c-KIT, platelet-derived growth factor receptor, and Raf/MEK/ERK signaling pathways [91-93]. Acting on multiple targets can not only inhibit tumor cell growth and differentiation but also inhibit tumor neovascularization [94] and improve treatment efficiency, so it can be used for the treatment of NSCLC and liver cancer [95].

Mammalian target of rapamycin (mTOR) inhibitors have been used as immunosuppressants for more than 10 years clinically [96], which is a serine/threonine protein kinase involved in regulating cell proliferation, growth, and metabolism [97, 98].

Other targeted antitumor drugs such as histone deacetylase inhibitors mainly control gene

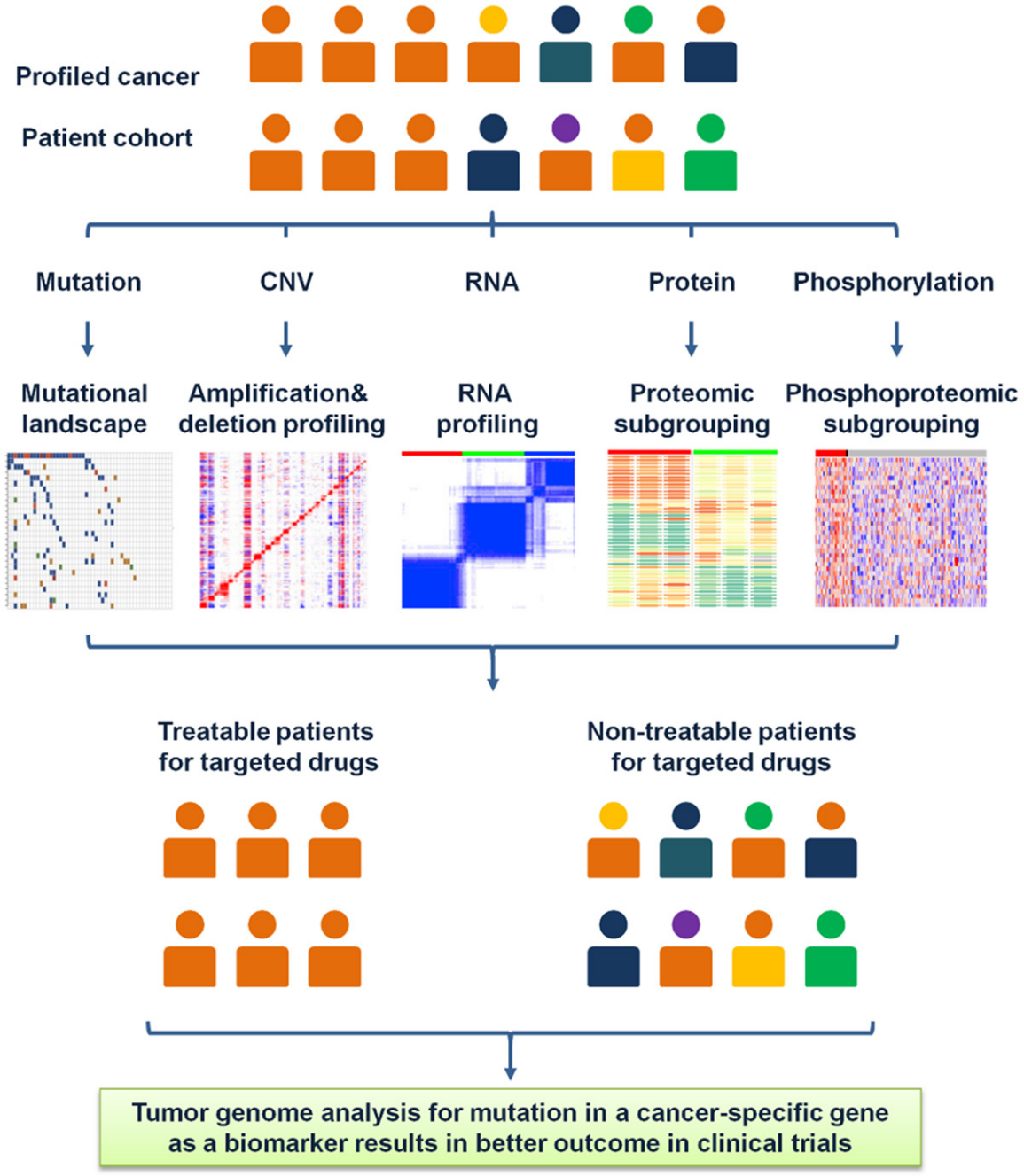

Figure 3. A road map to personalizing targeted cancer therapies using multinomial integration analysis. Multinomial integration analysis approach has been used for personalized targeted therapeutics in a genome profiled patient cohort. Mass spectrometry (MS)-based proteomics can measure global protein abundance and post-translational modifications to provide additional biological insights, which may not be deciphered by genomic analysis alone. The combination of sequencing and MS provides a more comprehensive picture linking cancer genotype to phenotype through functional proteomics and signaling networks. Integrated analyses of genomic, transcriptomic, proteomic, and phosphoproteomic data from tumor and matched non-tumor liver tissues revealed the connection and discordance among multi-omics and alterations in critical signaling and metabolic pathway. Thus, tumor genome analysis for mutation in a cancer-specific gene as a biomarker results in a better outcome in clinical trials.

expression by changing the histone acetylation degree, then changing the chromatin structure [99], which could induce tumor cell growth arrest, differentiation, and apoptosis to treat-tumors [100]. For example, the vorinostat of Merckwas the first histone deacetylase inhibi-

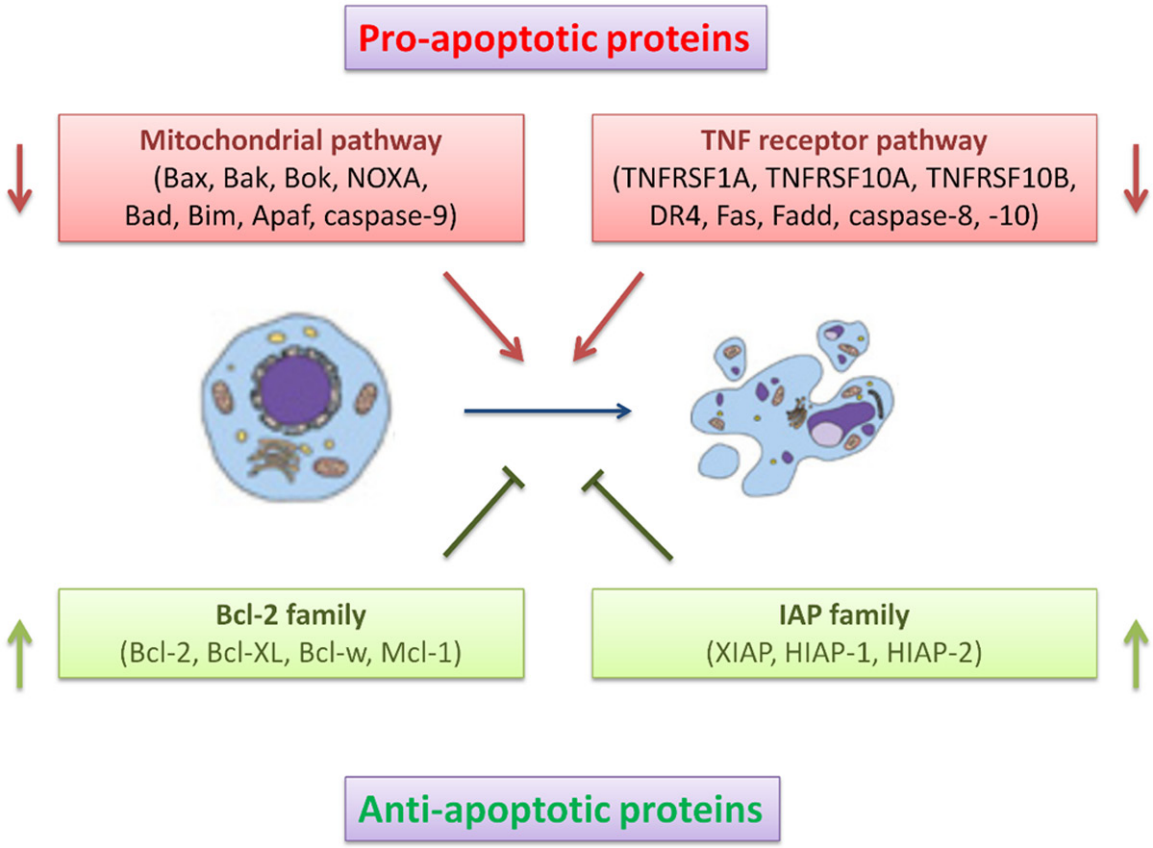

Figure 4. Status of proteins that participate in the apoptotic pathway in cancer. An overexpression of anti-apoptotic proteins has been reported, as well as a downregulation of pro-apoptotic proteins that participate in the mitochondrial apoptotic pathway and in the TNF receptor pathway. It has been suggested that the dysregulation of these proteins induces resistance to apoptosis in different therapeutic approaches.

tor approved by the US Food and Drug Administration in treating cutaneous T-cell lymphoma, marking a new approach to tumor therapy [101].

Autophagy is a catabolic process that leads to cellular degradation and the recycling of proteins and organelles by lysosomal digestion. Induced in starvation and several forms of stress rapidly, in which its dysregulation would join the processes like tumor. However, Apoptosis is a type of programmed cell death that cells are destroyed without releasing noxious substances into the surrounding area. Although the molecular mechanisms of apoptosis still need clarification, several proteins have been already known to have a vital role in regulating programmed cell death. It was proposed that therapeutic resistance in cancer is due to an upregulation of anti-apoptotic proteins and a downregulation of pro-apoptotic proteins, leading to genetic instability and the activation of oncogenes that favor cell survival and resistance to chemotherapy and recurrence (**Figure 4**).

Genetic engineering

At the end of the 20th century, a series of significant discoveries in cell and molecular biology promoted the biomedical technology development and many technological breakthroughs [102] including the found of wild-type tumor suppressor genes, suicide genes, anti-drug resistance genes and antisense oligonucleotides, and tumor genetically engineered bacteria tumors [103-105]. For example, Herceptin is a recombinant DNA-derived humanized monoclonal chimeric anti-p185HER-2 antibody [106] that can specifically bind to HER-2, downregulate it's gene, antagonize the growth-promoting effects of it's family, and mediate antibody-dependent cytotoxicity and anti-angiogenesis [107]. G3139 is an antisense oligo-

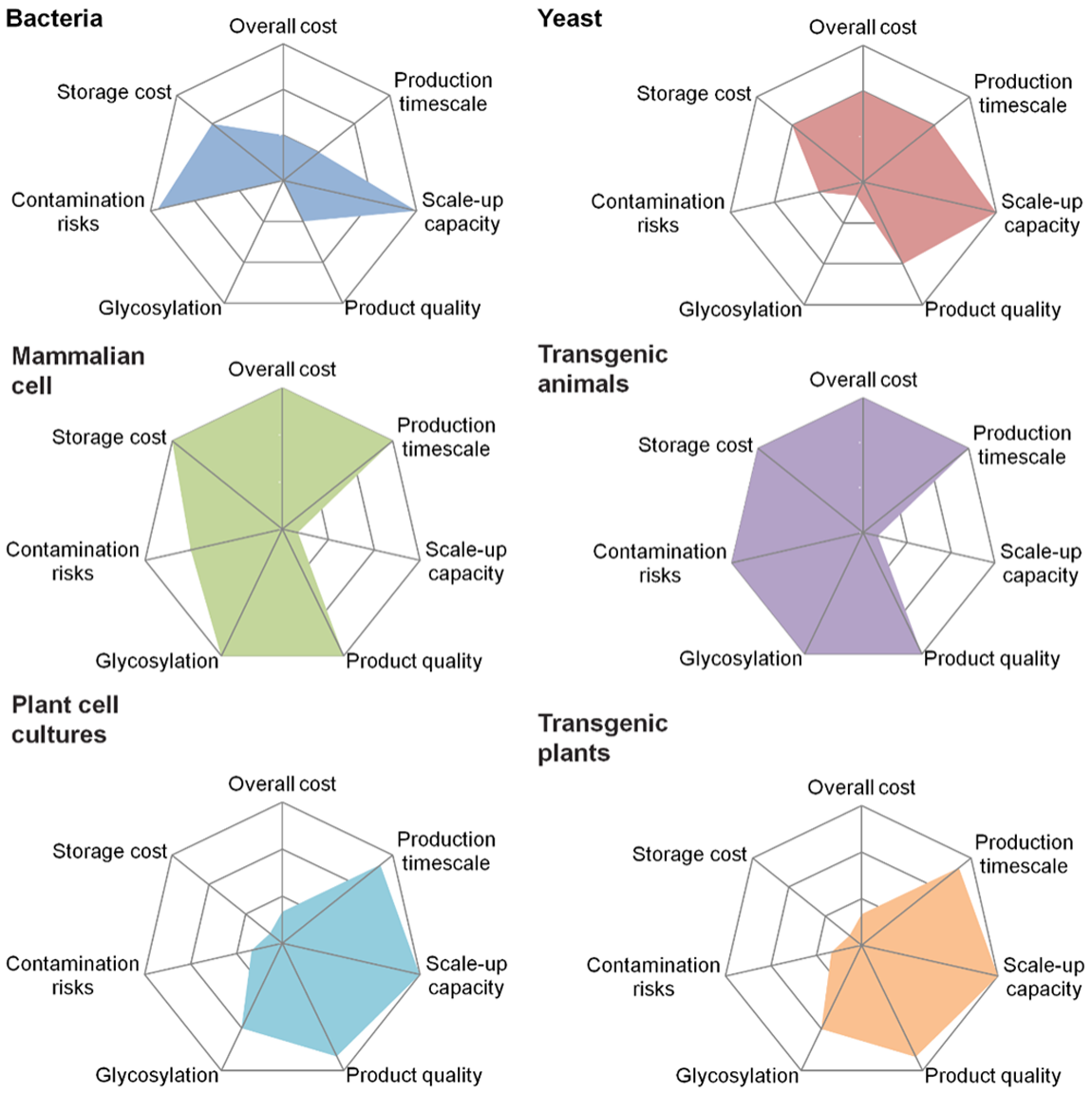

Figure 5. Comparison of sources and technologies for anti-cancer compounds. Traditional sources and new technologies that use microbial fermentation, insect and mammalian cell cultures, and transgenic animals have drawbacks in cost, scalability, product safety, and authenticity.

nucleotide drug against Bcl-2 [108, 109]. The renewal of these technologies have led to radical treatments for cancer (**Figure 5**).

In recent years, the development of molecular biology technology has been rapidly changed [110]. New cancer vaccine have become the focus, including genetically engineered cancer vaccines. Studies have shown that genetically modified tumor cells can kill cancer cells efficiently [111]. At present, the clinical application of cancer vaccines mainly focuses on the treatment of lung cancer, malignant melanoma, colon cancer, and certain hematological tumors [112, 113]. Therefore, the use of appropriate anticancer drugs for combination and sequential chemotherapy to achieve the goal of curing cancer or prolonging life is an optimized protocol.

Nanotechnology

Nanoparticles refer to particles between 1 and 100 nm in size, which havestrong adsorption capacity, large surface area, high catalytic efficiency, and high surface reactivity [114]. It is a new way to deliver anticancer drugs. Particles >200 nm in tissue are easily phagocytized by

the phagocytic system, whereas magnetic particles <100 nm are more easily adsorbed and deposited at a lower rate, facilitating diffusion to tissues are widely used in antitumor drugs [115]. The properties exhibited by nanomaterials indicate anopolymer material showed broad anticancer application.

Other ways

With the further research of physiological and biochemical mechanisms, some drugs known as prototype drugs have achieved great success in medical effects and in the pharmaceutical market [117]. Many drugs with intellectual property rights have emerged, and those drugs with the same efficacy are called "me-too" drugs [118], the research of it is to find similar chemical structures that are not protected by patents [119]. Researchers change local chemical structures, increase water solubility or fat solubility, and bioavailability [120]. Those drugs would cause metabolic transformation *in vivo*, prolonging the duration of action, which are sometimes better than the original drug, reducing side effects and adverse reactions to some extent [121]. For example, Melphalan (sarcolysin), with phenylalanine as the carrier, has a better effect on malignant tumors [122]. Formylmerphalan is obtained by subjecting NH2 to formylation on the basis of melphalan [123], comparing with sarcolysine, it has higher therapeutic index and lower toxicity [124]. These drugs have followed the development ideas, mechanism of action, and targets of innovative drugs [125], and have modified the listed drugs in chemical structure, circumventing patent infringement with low research difficulty, low investment, and low risk. It is a way researching on new drugs, and it is also a shortcut to create a transition [126].

Old drugs refer to drugs that have been put on the market for clinical application and are known to everyone, Basedon previous research and development, detailed molecular structure, mechanism of action, and safety information [127]. "Me-too" dugs means shortening the development cycle of small molecule drugs, reducing risks, and increasing the success rate of small molecule drug development, enabling faster entry into clinical trials and rapid phase II clinical trials [128]. The assessment is reported to save approximately 40% of the cost and shorten the development cycle to 3 to 12 years [129, 130].

Challenges and opportunities

Since the 20th century, people havn't paid much attention to oncology drug research. Traditional cytotoxic drugs are still the main body of cancer drug therapy. However, with the development of molecular oncology and molecular pharmacology, the nature of tumor is gradually being clarified. The application of advanced technologies such as large-scale rapid screening, combinatorial chemistry, and genetic engineering have accelerated the drug development process [131, 132].

However, at present, the development of small molecule drugs has reached a bottle neck, which is not only reflected in the floating number of new drugs on the market, but also in the increasing number of pharmaceutical R & D enterprises invest without breakthrough. For small molecule drugs, it is a matter of time to catch up or surpass. In the next few decades, the market share of large molecule drugs will be higher, gradually surpassing small molecule drugsbut does not mean that small molecule drugs will disappear. It just means that such drugs will start to move forward steadily rather than speedily [133-135].

Conclusion

Although therapeutic drugs have been discovered by this traditional method, there are still problems such as unpredictability, blindness, and resource inefficiency. When life sciences enter the post-genome era, scientists will discover new genes from a large number of gene sequencing results, delve into their functions and regulatory networks, andimprove the quality and efficiency of innovative drug research through a large number of bioinformatics libraries, compound information libraries and biochips.

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Disclosure of conflict of interest

None.

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