Review Article

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Challenges to Cure Cancer

Sudha Bansode*

Associate Professor in Zoology, Shankarrao Mohite College, Akluj, Maharashtra State, India

***Corresponding author**
Dr. Sudha Bansode, Associate Professor in Zoology, Shankarrao Mohite College, Akluj, Maharashtra State, India, E-mail: drsudhabanasode@yahoo.com

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Abstract

Cell division is a normal process in multicellular organisms. Growth and repair (replacement of dead cells) take place as a result of cell division (mitosis). Except for cells like the liver and brain cells, which rarely divide in the mature adult, most cells undergo frequent division. Sometimes, however, cell division becomes very rapid and uncontrolled, leading lo cancer. It should be clearly understood that rapid growth means a high rate of cell division for a particular cell type. It is possible for perfectly normal cells, e. g. the blood-forming cells, to have a higher rate of division than some cancerous cells.

Cells which undergo rapid, abnormal and uncontrolled growth at the cost of remaining ceils are called neoplastic cells. The growths resulting from the division of such cells are called neoplastic growths or tumours. Tumours are commonly classified as benign and malignant. Abnormal and persistent cell division that remains localized at the spot of origin results in the so-called benign tumours. It should be noted, however, that benign tumours can sometimes be fatal, e'g, brain tumours that cause pressure on vital centres. Benign tumours usually contain well-differentiated cells. Tumour cells may be carried by the blood stream, or the lymphatic system, or by direct penetration to other parts of the body, where they may induce secondary (metastatic) tumours. Such invasive cancers ultimately result in the death of the organism and are therefore said to be malignant. Malignant tumours usually contain undifferentiated cells, often with large nuclei and nucleoli.

Types of Cancer

Cancer is not one single disease but a complex of many diseases. About two hundred distinct types of cancer have been recognized. These can be grouped into four main types: carcinomas, sarcomas, lymphomas and leukemias.

1. **Carcinomas are tumors made** are tumours mude up principally of epithelial cells of ectodermal or endodermal origin. The solid tumours innerve tissue and in tissues of body surfaces, or their attached glands, are examples of carcinomas. These include cervical, breast, skin and brain carcinomas. About 85 per cent of cancers are carcinomas.
2. **Sarcomas** are tumours made up principally of connective tissue cells, which are of mesodermal origin. They are solid tumours growing from connective tissue, cartilage, bone and muscle. Although they account for most of the cancers studied in laboratory animals, they constitute only about 2 per cent of human cancers.
5. **Lymphomas** are cancers in which there is excessive production of lymphocytes by the lymph nodes and spleen. Hodgkin's disease is an example of a lymphoma. Lymphomas constitute about 5 percent of human cancers.
4. **Leukemias** are neoplastic growths of leucocytes (W. B. C), and are characterized by excessive production of the cells. They constitute about 4 per cent of human cancers.

In addition to the types of cancer mentioned above there may be mixed malignant tumours, e. g. tumours arising from both ectodermal lnd mesodermal tissues.

Characteristics of Cancer Cells

Almost all types of differentiated cells can become neoplastic or cancerous. The process of cell change in which a cell loses its ability to control its rate of division, and thus becomes a tumour cell, is called cell transformation. The cancerous cell generally retains the- structural and functional characteristics of the normal cell type from which it is derived. Thus cancerous cells of the thyroid gland continue to secrete thyroxin. Neoplastic cells, however, differ from their normal counter parts in several respects.

1. **Immortalization:** Normal cell cultures do not survive indefinitely. For example, human cell cultures die after about 50 generations, and chicken cell cultures have a much shorter life expectancy. On the other hand transformed cell cultures are immortal and can grow indefinitely. Cell cultures infected with mouse sarcoma virus can be maintained as long as nutrition is provided and overcrowding avoided.
2. **Ioss of contact inhibition:** Normal cells in a culture stop growingwhen their plasma membranes come into contact with one another. When two normal cells come into contact, one or both will stop moving and then begin to move in another direction. This inhibition of growth after contact is called contact inhibition.

Hypotheses about Cancer

There are several hypotheses to explain why a cell becomes cancerous. The principal hypotheses that will be considered here are the somatic mutation hypothesis, the viral genes hypothesis and the defective immunity hypothesis.

I. The Somatic Mutation Hypothesis

According to this hypothesis cancer is the result of somatic mutations (i.e. mutations not involving germ cells), without viral infection occurring in g cell. Such a mutation may alter the control mechanism of the cell, leading to unregulated division or cancer. The mutations may involve the activation of normally repressed genes. This could take place by (i) mutations in the repressed genes themselves, or (ii) mutations that block the production of repressor proteins, thus unblocking inactive genes and making them active.

Most cancerous cells have abnormal chromosomal components. Often there are different. numbers of chromosomes in different cells of one tumour. In patients with chronic myeloid leukemia a large part of the long arm of chromosome number 22 is lost. Such chromosomes are called Philadelphia chromosomes. Chromosomal abnormality is found in the bone marrow of 90 percent patients suffering from chronic myeloid leukemia. An elongated chromosome number 9 has also been reported from chronic myeloid leukemia patients. Possibly a piece has broken of from chromosome number 22 and translocated to number 9. In patients with retinoblastoma the middle segment of chromosome 13 is missing. It is possible, however, that the cases mentioned above could be the consequences or accompaniments of cancer rather than its cause. The evidence for chromosomal alteration as a cause of cancer does not look strong.

Sachs and his group have postulated that cells contain effector (E) chromosomes which cause malignancy and supressor (S) chromosomes which suppress malignancy. Whether a cell is malignant or not depends upon a balance in the number of E and S chromosome. It has been suggested that in the hamster karyotype chromosomes. It has been suggested that in the hamster karyotype chromosome 5_7 is the E chromosome, chromosome 7_3 the S chromosome for transformation and chromosome 7_2 the S chromosome for malignancy. Chromosomal changes in hamster cells after treatment with polycyclic aromatic hydrocarbons (PAH) suggest that the modifications may be important in oncogenic transformation (Benedict, 1972). On the other, hand studies of chromosomal changes by DiPaolo and his co-workers (1969, 1971, 1973, 1974) led them to conclude that the chromosomal changes were random and not directly concerned with transformation. At present the role of chromosomal changes in malignant transformation is debatable.

Targeted therapies differ from standard chemotherapy in several ways:

- Targeted therapies act on specific molecular targets that are associated with cancer, whereas most standard chemotherapies act on all rapidly dividing normal and cancerous cells.
- Targeted therapies are deliberately chosen or designed to interact with their target, whereas many standard chemotherapies were identified because they kill cells.
- Targeted therapies are often cytostatic (that is, they block tumor cell proliferation), whereas standard chemotherapy agents are cytotoxic (that is, they kill tumor cells).

Targeted therapies are currently the focus of much anticancer drug development, They are a cornerstone of precision medicine, a form of medicine that uses information about a person's genes and proteins to prevent, diagnose, and treat disease.

Many targeted cancer therapies have been approved by the Food and Drug Administration (FDA) to treat specific types of cancer. Others are being studied in clinical trials (research studies with people), and many more are in preclinical testing (research studies with animals).

The ability of intracellular signaling networks to integrate and distribute regulatory information requires that individual signaling proteins must act as nodes, responding to multiple inputs and regulating multiple effector outputs. One of the major advances in the last decade has been the recognition that many signaling proteins contain modular protein domains that mediate protein-protein interactions. These interaction modules serve to target signaling proteins to their substrates or to specific intracellular locations, to respond to posttranslational modifications, such as phosphorylation, acetylation and methylation, and to link polypeptides into multiprotein signaling complexes and pathways (Pawson and Nash, 2003). The same protein modules can also mediate intramolecular interactions that regulate signaling function, and a frequent theme is that upstream regulators may act by promoting or disrupting these intramolecular interactions. Thus, to understand the overall architecture of the signaling network, we will ultimately need to identify all of these inter- and intramolecular interantions.

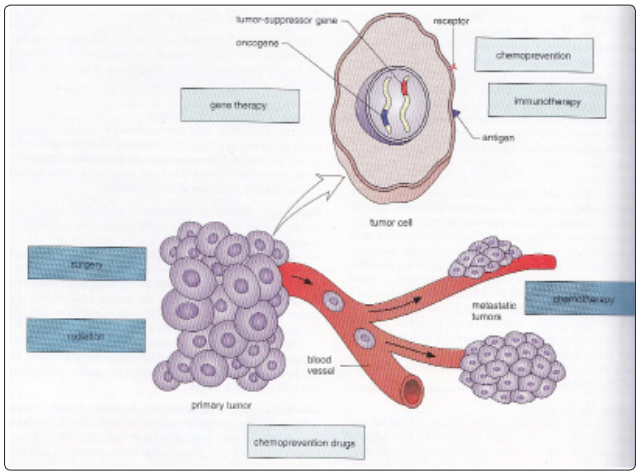

Figure 1: Treatment of Cancer – In standard use (dark-blue) surgery and radiation are used to rid the body of localized tumor.

Chemotherapy is more effective and used when the cancer has metastasized. Future therapies (light blue) include immunotherapy, gene therapy, chemoprevention immunotherapy zeros in plasma membrane receptors and antigens as a way to identify cancer cells.

Gene therapy corrects he gene type of cancer cells and chemoprevention prevents metastatis and angiogenesis. The ultimate feat would be prevents the occurance of cancer in the first place.

Signaling inhibitors as cancer therapeutics

Transformation of fibroblasts by activated oncogenes such as Ras is dependent on multiple pathways, and in some instances, inhibition of a single one of these pathways can inhibit transformation. If this is a valid model for carcinogenesis, single signaling inhibitors

might be effective cancer therapeutics. However there are also precedents for believing that effective inhibition of some aspects of transformation may require multiple inhibitors. The synergy between metalloproteinase inhibitors and ROCK inhibitors in inhibiting tumor cell invasion, as described by Chris Marshall (see above), represents one such precedent. Moreover, as argued earlier, because tumor cells are genetically unstable and continually evolving, they may be able to evade blockade of a single pathway so that effective therapies may require the use of multiple inhibitors, or the use of signaling inhibitors as supplements to therapy with conventional DNA-damaging agents.

Raf proteins are under active investigation as therapeutic targets. There are three isoforms of Raf in mammals, Raf-1, B-Raf, and A-Raf. Mutations in the activation loop of B-Raf that activate catalytic activity have recently been found to occur in some 66% of melanomas and at a lower frequency in other cancers (Davies et al., 2002). The most common mutation is V599E, and this mutant form of Raf is transforming for NIH-3T3 cells. Maria Karasarides (lnstitute of Cancer Research, Landon) reported that transformation can be blocked by RNAi downregulation of B-Raf or by MFK inhibitors. Furthermore, downregulation of B-Raf in melanoma cells results in caspase 3 activation and apoptosis. Frank McCormick (University of California. San Francisco) discussed the therapeutic potential of a Raf inhibitor developed at the Bayer Corporation. Starting with a lead structure with an lC50 for Raf inhibition of 17 μM, the Bayer group, using combinatorial chemistry, developed an orally active compound, BAY43-9006, which has an lC50 for Raf inhibition of 12 nM. This inhibitor blocks MEK phosphorylalion by mutant B-Raf. Phase l trials suggest that the inhibitor may induce a partial response or stabilize disease progression when administered as single agent in the treatment of renal cell carcinoma or when used in combination with carboplatin and paclitaxel for the treatment of melanomas. These exciting but still preliminary findings suggest that Raf activity is a promising target for therapeutic intervention.

STI-571 (Gleevec) has proven extremely effective in the treatment of chronic myelogenous leukemia, in which Abl is activated by translocation, and is also effective in the treatment of gastrointestinal stromal tuntors, in which there are mutations in either c-Kit or the PDGF receptor o. Carl-Henrik Heldin (Ludwig lnstitute for Cancer Research, Uppsala, Sweden) described other uses of STI-571 as a PDGF receptor antagonist (Pietras et al., 2003). One such use is in the treatment of dermatofibrosarcoma protuberans, a disease of intermediate malignancy. It results from a fusion of the collagen 1A1 gene to the gene encoding the PDGF-B chain: the fusion gene product is processed to generate PDGF-B chain. STI-571 reduces the growth of subcutaneous dermatofibrosarcoma tumors in a xenograft model. Clinical trials suggest that STI-571 can induce tumor regression. Another use of STI-571 as. A cancer therapeutic stems from its effect on tumor stromal cells, which frequently express PDGF receptors. Activation of stromal PDGF-R causes an increase in tumor interstitial fluid pressure, which reduces the uptake of chemotherapeutic drugs. Heldin demonstrated that STI-571 reduces tumor interstitial fluid pressure and thereby increases the uptake and efficacy of drugs such as taxol and 5-FU (Pietras et al., 2002).

The response of a tumor cell to an inhibitor or drug depends on its particular genetic an epigenetic status. Tumor cells acquire resistance to apoptosis during the course of tumor progression, and enhanced survival signaling may be important in promoting resistance to chemotherapeutic agents (Johnstone et al., 2002) for example, Scott Lowe (Cold Spring Harbor Laboratory. New York) reported that the introduction of various antiapoptotic lesions (e.9., p53 loss, or overexpression of Bcl-2 or Akt) in Eμ-Myc transgenic mice enhances lymphomagenesis and the chemoresistance of the lymphomas. Interestingly, the nature of the antiapoptotic iesion can have an impact on how the lymphoma responds to a combination of conventional and targeted agents. Thus, knowledge of apoptosis resistance mechanisms in cancer may allow the tailoring of therapies for individual patients. With this in mind, Lowe described the use of short-hairpin RNA libraries to identify genes that either sensitize or inhibit drug-induced apoptosis. In the same context, Margaret Frame and Caroline Dive (University of Manchester) reported that catalytically inactive mutants of Src sensitize metastatic colon cancer ceils to oxaliplatin- and Fas-induced apoptosis. These src mutants might act as either adaptor proteins or dominant-negatives and might either inhibit an antiapoptotic pathway or promote a proapoptotic pathway.

The findings described at this meeting indicate that our understanding of signaling pathways has advanced to the point where specific targets for therapeutic intervention can be identified. However, we need to understand how whole signaling networks function within the context of the intact cell if we are to develop rational strategies based on the genetic alterations of individual cancers. Based on the pace of the progress reported at this meeting, it is safe to predict that the next few years should see exciting new developments in targeted cancer therapies.

Abnormal Notch Signaling Activation and CSCs

Abnormal activation of Notch signaling plays a pivotal role in the CSCs of breast cancer, pancreatic cancer, and glioblastoma. For instance, Barnawi et al. reported that fascin (an actin-bundling protein) effectively regulates breast CSCs at least partially through Notch pathway [78]. Fascin knockdown significantly reduced breast stem cell-like phenotype (downregulation of stem cell pluripotent genes such as Oct4, Nanog, Sox2, and Klf4), and the cells became less competent in forming colonies and tumorspheres. Conversely, activation of Notch signaling induced the relevant downstream targets predominantly in the fascin-positive cells, and fascin-positive CSCs showed stronger tumorigenesis. In another study, immunohistochemical analysis of 115 breast tumor tissues from primary lesions was performed, and results showed that Notch positive tissues were significantly associated with a CSC marker aldehyde dehydrogenase I family member Al levels. Very recently, Choy et al. reported that Notch 3 signaled constitutively in a panel of basal breast cancer cell lines and in more than one-third of breast basal tumors.

Moreover, the important role of Notch signaling was also demonstrated in several other types of CSCs. In a study of patient-derived pancreatic CSCs, Notch ligands Notch 1, Notch 3, Jagl, Jag2, and Notch target gene Hes l were found to be highly expressed in the pancreatic CSCs, and an inhibitor of y-secretase (an important protease mediating Notch signaling by releasing the Notch I CD) significantly decreased the CSC's subpopulation and tumorsphere formation [81]. Moreover, activation of Notch signaling by delta/Serrate/Lag-2 peptide or inhibition of the signaling by knockdown of Hes l enhanced or decreased pancreatic CSC's tumorsphere formation, respectively [81]. In addition, Notch signaling dysregulation has also been recognized in glioblastoma CSCs [82].

It was found that Protein Kinase C Iota (PKCi) was highly expressed in glioblastoma patientderived CSCs, and silencing PKCi resulted in apoptosis and reduction of proliferation of the glioblastoma CSCs in vitro and tumor growth in vivo in a xenograft mouse model. Gene expression profiling of PKCi-silenced glioblastoma CSCs revealed a novel role of the Notch signaling pathway in PKCi mediated glioblastoma CSC's survival. In addition to its important roles in CSCs, Notch signaling is also involved in EMT to promote cancer cell acquisition of a stem-like phenotype and drug resistance. For instance, prostate cancer cells undergoing EMT displayed stem-like cell features characterized by increased expression of Notch 1 and other pluripotent genes such as Sox2, Nanog. Oct4, and Lin28.

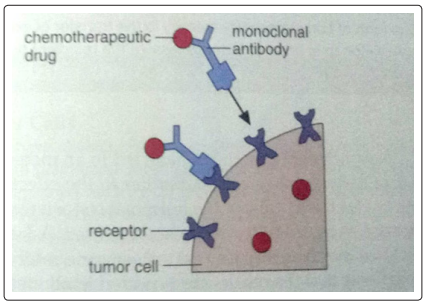

Figure 2: Immunotherapy

Therapeutic Agents Targeting Notch Signaling

Therapeutics targeting the Notch pathway mostly consist of y-secretase inhibitors and anti-DLL4 antibqdies. Inhibition of the Notch pathway via y-secretase inhibitors prevents Notch receptor cleavage at the cell surface, thus blockrng activation of self-renewal target genes. ln a preclinical study, a y-secretase inhibitor RO4929091 significantly suppressed Notch target genes Hes1, Hey1, and HeyL [85]. Several phase I and phase II studies have been conducted in hopes of synergistically utilizing RO4929097 with other agents for cancer treatment. For instance, in a completed phase I trial, RO4929097 and Cediranib Maleate were used in tandem to determine the phase II dose and safety profile of RO4929097 in solid tumors (NCT Number: NCT01131234), and the clinical trial data shall be announced soon. Another y-secretase inhibitor is LY900009, developed by Eli Lilly, which is in phase I for patients with advanced cancer including leiomyosarcoma and ovarian cancer. A third y-secretase inhibitor (PF-003084014) was developed by Pfizer, and it is progressing in its phase I trials in patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma. In addition to y-secretase inhibitors, another category of Notch pathway molecules is monoclonal antibodies that target DLL4 (Delta-like ligand 4) to prevent ligand binding. Enoticumab (REGN42L) is an anti-DLL4 antibody that has been used to target advanced solid tumors with overexpression of DLL4 (such as ovarian cancer) [88]. In 2015, a recommended phase II dose of 4 mg /kg every 3 weeks or 3 mg/kg every 2 weeks administered intravenously was established based on PK profiles in patients diagnosed with ovarian, colon, or breast cancer. Another anti-DLL4 monoclonal antibody developed by OncoMed Pharmaceuticals and Celgene is Demcizumab, which has recently completed a phase I dose escalation clinical trial as well. In this study, Demcizumab was well tolerated at doses <5 mg with disease stabilization and tumor size decreases when administered weekly. The side effects of Demcizumab include hypertension and an increased risk of congestive heart failure in prolonged drug administration (NCT Number: NCT Number: NCT02722954).

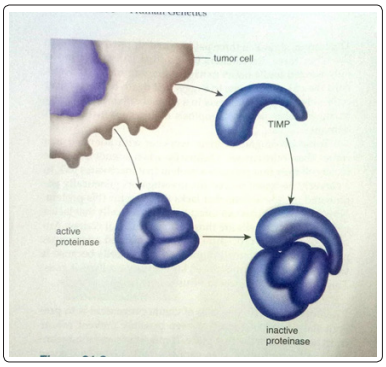

Figure 3: Chemoprevention

Cancer cells produce Proteinase enzymes that allow them to mestasize and TMP, a Proteinase inhibitor, perhaps it would be possible to isolate produces administer the TMP to cancer proteins. In this way matastasis would be prevented.

Crosstalk among Pathways and Combination Treatments

Many pathways do not act as isolated units but rather often interact with other pathways as a biological network during development and homeostasis. Crosstalk among Wnt, HH, Notch, and other pathways have been reported in cancer and CSCs. For instance, in a colorectal cancer study, progastrin secreted by colorectal tumors was shown to activate Wnt signaling and result in expression of Wnt target genes including Jagged-1, one Notch ligand. Upregulation of Jagged-1 induces Notch signaling which in turn may further elevate B-catenin activity of progastrin-driven Wnt and Notch signaling in colorectal cancer cells. Similarly, in breast CSCs, Mel-18 was reported as a negative regulator of breast CSC's self-renewal. Knockdown of Mel-18 increased Wnt signaling, which subsequently upregulated Wnt target gene jagged-1's expression, leading to activation of the Notch pathway for CSC's self-renewal [93]. In addition, HH signaling can crosstalk with both Wnt and Notch pathways as well. In gastric cancer cells, HH signaling was shown to suppress Wnt signaling through the soluble frizzled-related protein 1 (sFrP1), a target gene of HH signaling capable of modulating Wnt pathway by directly binding to Wnt ligands. In another study of glioblastoma cells and patient specimens, Notch signaling inhibition was shown to downregulate its target gene Hes 1 which in turn upregulates GLI transcription in the HH pathway.

Complex signaling networks are known to contribute to the cellular diversity of stem cells during embryogenesis and tissue homeostasis and may play essential roles in the cancer and CSC's biology. In recent years, significant efforts have been made to develop combination therapies to target multiple signaling pathways for cancer treatments. For instance, a recent study demonstrated that combination inhibition of both Notch and HH signaling depleted the CSC subpopulation cells in a prostate cancer model. In addition, a clinical trial of combination of HH pathway inhibitor Vismodegib and Notch signaling inhibitor RO4929097 has bee conducted in patients with advanced breast and 'sarcoma. In another recent study, Sharma et al. showed that combination treatment with HH signaling inhibitor NVP-LDE225 and pI3/mTOR/Akt signaling inhibitor NVPBEZ235 inhibited self-renewal capacity of pancreatic CSCs by suppressing the expression of pluripotency maintaining factors Nanog, Oct-4, Sox-2, and c-Myc and transcription of GLI.

How are targets for targeted cancer therapies identified?

The development of targeted therapies requires the identification of good targets-that is, targets that play a key role in cancer cell growth and survival. (lt is for this reason that targeted therapies are sometimes referred to as the product of "rational" drug design.)

One approach to identify potential targets is to compare the amounts of individual proteins in cancer cells with those in normal cells. Proteins that are present in cancer cells but not normal cells or that are more abundant in cancer cells would be potential targets, especially if they are known to be involved in cell growth or survival. An example of such a differentially expressed target is the human epidermal growth factor receptor 2 protein (HER-2). HER-2 is expressed at high levels on the surface of some cancer cells. Several targeted therapies are directed against HER-2, including trastuzumab (Herceptin®), which is approved to treat certain breast and stomach cancers that overexpress HER-2. Another approach to identify potential targets is to determine whether cancer cells produce mutant (altered) proteins that drive cancer progression. For example, the cell growth signaling protein BRAF is present in an altered form (known as BRAFV600E) in many melanomas. Vemurafenib (Zelboraf®) targets this mutant form of the BRAF protein and is approved to treat patients with inoperable or metastatic melanoma that contains this altered BRAF protein.

Researchers also look for abnormalities in chromosomes that are present in cancer cells but not in normal cells. Sometimes these chromosome abnormalities result in the creation of a fusion gene (a gene that incorporates parts of two different genes) whose product, called a fusion protein, may drive cancer development. Such fusion proteins are potential targets for targeted cancer therapies. For example, imatinib mesylate (Gleevec®) targets the BCR-ABL fusion protein, which is made from pieces of two genes that get joined together in some leukemia cells and promotes the growth of leukemic cells.

How are targeted therapies developed?

Once a candidate target has been identified, the next step is to develop a therapy that affects the target in a way that interferes with its ability lo promote cancer cell growth or survival. For example, targeted therapy could reduce the activity of the target or prevent it from binding to a receptor that normally activates, among other possible mechanisms.

Most targeted therapies are either small molecules or monoclonal antibodies. Small-molecule compounds are typically developed for targets that are located inside the cell because such agents are able to enter cells relatively easily. Monoclonal antibodies are relatively large and generally cannot enter cells, so they are used only for targets that are outside cells or on the cell surface.

Candidate small molecules are usually identified in what are known as "high-throughput screens," in which the effects of thousands of test compounds on a specific target protein are examined. Compounds that affect the target (sometimes called "lead compounds") are then chemically modified to produce numerous closely related versions of the lead compound. These related compounds are then tested to determine which are most effective and have the fewest effects on nontarget molecules.

Monoclonal antibodies are developed by injecting animals (usually mice) with purified target proteins, causing the animals to make many different types of antibodies against the target. These antibodies are then tested to find the ones that bind best to the target without binding to nontarget proteins.

Before monoclonal antibodies are used in humans, they are "humanized" by replacing as much of the mouse antibody molecule as possible with corresponding portions of human antibodies. Humanizing is necessary to prevent the human immune system from recognizing the monoclonal antibody as "foreign" and destroying it before it has a chance to bind to its target protein. Humanization is not an issue for small-molecule compounds because they are not typically recognized by the body as foreign.

How is it determined whether a patient is a candidate for targeted therapy?

For some types of cancer, most patients with that cancer will have an appropriate target for a particular targeted therapy and, thus, will be candidates to be treated with that therapy. CML is an example: most patients have the BCR-IBL fusion gene. For other cancer types, however, a patient's tumor tissue must be tested to determine whether or not an appropriate target is present. The use of a targeted therapy may be restricted to patients whose tumor has a specific gene mutation that codes for the target; patients who do not have the mutation would not be candidates because the therapy would have nothing to target.

Sometimes, a patient is a candidate for a targeted therapy only if he or she meets specific criteria (for example, their cancer did not respond to other therapies, has spread, or is inoperable). These criteria are set by the FDA when it approves a specific targeted therapy.

What are the limitations of targeted cancer therapies?

Targeted therapies do have some limitations. One is that cancer cells can become resistant to them. Resistance can occur in two ways: the target itself changes through mutation so that the targeted therapy no longer interacts well with it, and/or the tumor finds a new pathway to achieve tumor growth that does not depend on the target.

For this reason, targeted therapies may work best in combination. For example, a recent study found that using two therapies that target different parts of the cell signaling pathway that is altered in melanoma by the BRAFV600E mutation slowed the development of resistance and disease progression to a greater extent than using just one targeted therapy.

Another approach is to use a targeted therapy in combination with one or more traditional chemotherapy drugs. For example, the targeted therapy trastuzumab (Herceptin®) has been used in combination with docetaxel, a traditional chemotherapy drug, to treat women with metastatic breast cancer that overexpresses the protein HER2/neu.

Another limitation of targeted therapy at present is that drugs for some identified targets are difficult to develop because of the target's structure and/or the way its function is regulated in the cell. One example is Ras, a signaling protein that is mutated in as many as one-quarter of all cancers (and in the majority of certain cancer types, such as pancreatic cancer). To date, it has not been possible to develop inhibitors of Ras signaling with existing drug development technologies. However, promising new approaches are offering hope

that this Iimitation can soon be overcome.

What are the side effects c:f targeted cancer therapies?

Scientists had expected that targeted cancer therapies would be less toxic than traditional chemotherapy drugs because cancer cells are more dependent on the targets than are normal cells. However, targeted cancer therapies can have substantial side effects.

The most common side effects seen with targeted therapies are diarrhea and liver problems, such as hepatitis and elevated liver enzymes. Other side effects seen with targeted therapies include:

- Skin problems (acneiform rash, dry skin, nail changes, hair depigmentation)
- Problems with blood clotting and wound healing
- High blood pressure
- Gastrointestinal perforation (a rare side effect of some targeted therapies)

Certain side effects of some targeted therapies have been linked to better patient outcomes. For example, patients who develop acneiform rash (skin eruptions that resemble acne) while being treated with the signal transduction inhibitors erlotinib (Tarceva®) or gefitinib (lressa®), both of which target the epidermal growth factor receptor, have tended to respond better to these drugs than patients who do not develop the rash. Similarly, patients who develop high blood pressure while being treated with the angiogenesis inhibitor bevacizumab generally have had better outcomes.

The few targeted therapies that are approved for use in children can have different side effects in children than in adults, including immunosuppression and impaired sperm production

What targeted therapies have been approved for specific types of cancer?

The FDA has approved targeted therapies for the treatment of some patients with the following types of cancer (some targeted therapies have been approved to treat more than one type of cancer):

Adenocarcinoma of the stomach or gastroesophageal junction: Trastuzumab (Herceptin®), ramucirumab (Cyramza®)

Bladder cancer: Arezolizumab (TecentriqTm), nivolumab (Opdivo®), durvalumab (lmfinzi ™), avelumab (Bavencio ®), pembrolizumab (Keytruda ®)

Brain Cancer: Bevacizumab (Avastin ®), everolimus (Afinitor®)

Breast Cancer: Everolimus (Afinitor®), tamoxifen (Nolvadex), toremifene®), Trastuzumab (Herceptin®), fulvestrant (Faslodex®), anastrozole (Arimidex®), exemestane (Aromasin®), lapatinib (Tykerb®), letrozole (Femara®), pertuzumab (Perjeta®), ado-trastuzumab emtansine (kadcyla®). Palbociclib (Ibrance®), ribociclib (Kisqali®), neratinib maleate (Nerlynx™)

Cervical cancer: Bevacizumab (Avastin®)

Colorectal cancer: Cetuximab (Erbitux®) Panitumumab (Vectibix®), bevacizumab (Avastin ®), zivaflibercept (Zaltrap®), regorafenib (Stivarga®), ramucirumab (Cyramza®), nivolumab (Opdivo®)

Dermatofibrosarcoma protuberans: Imatinib mesylate (GIeevec,®)

Endocrine/neuroendocrine tumors: Lanreotide acetate (Somatuline® Depot), avelumab Bavencio ®)

Head and neck cancer: Cetuximab (Erbituxi®), pembrolizumab (Keytruda®), nivolumab (Opdivo®)

Gastrointestinal stromal tumor: Imatinib mesylate (Gleevec®), sunitinib (Sutent®), regorafenib (Stivarga®]

Giant cell tumor of the bone: Denosumab (Xgeva®)

Kidney cancer: Bevacizumab (Avastin®), sorafenib (Nexavar®), sunitinib (Sutent®), pazopanib (Votrient®), temsirolimus (Torisel®), everolimus (Afinitor®), axirinib (lnlyta®), nivolumab (Opdivo®), cabozantinib (CabometyxTm), lenvatinib mesylate (Lenvima®)

Leukemia: Trerinoin (Vesarroid®), imalinib mesylate (Gleevec®), dasatinib (Sprycel®), nilotinib (Tasigna®), bosutinib (Bosulif®), rituximab (Rituxan®), alemtuzumab (Campath®), ofatumumab (Arzerra®), obinutuzumab (Gazyva®), ibrutinib (lmbruvica®), idelalisib (Zydelig®), blinatumomab (blincyto®), venetoclax (Venclexta™), ponatinib hydrochloride (lclusig®), midostaurin (Rydapt®), enasidenib mesylate (Idhifa®)

Liver cancer: Sorafenib (Nexavar®), rergorafenib (Stivarqa®)

Lung cancer: Bevacizumab (Avastin®), crizotinib (Xalkori®), erlotinib (Tarceva®), gefitinib (lressar®), afatinib dimaleate (Gilotrif®), ceritinib (LDK378/Zykadia™), ramucirunrab (Cyramza®), nivolumab (Opdivo®), pembrolizumab (Keytruda®), osimertinib (Tagrisso™), necitumumab (Portrazza™), alectinib (Alecensa®), atezolizumab (Tecentriq™), brigatinib (Alunbrig™), trametinib (Mekinist®), dabrafenib (Tafinlar®)

Lymphoma: Ibritumomah tiuxetan (Zevalin®), denileukin diftitox (Ontark®), brentuximab vedotin (Adcetris®), rituximab (Rituxan®), vorinostat (Zolinza®), romidepsin (lstodax®), bexarotene (Targretin®), bortezomib (Velcade®), pralatrexate (Folotyn®), ibrutinib (lmbruvica®), siltuximab (Sylvant®), idelalisib (Zydelig®), belinostat (Beleodaq®), obinutuzumab (Gazyva®), nivolumab (Opdivo®), pembrolizumab (Keytruda®)

Microsatellite instability-high or mismatch repair-deficient solid tumors: Pembrolizumab (Keytruda®)

Multiple myeloma: Bortezomib (Velcade®), carfilzomib (Kyprolis®), panobinostat (Farydak®), daratumumab (Darzalex™), ixazomib citrate (Ninlaro®), elotuzumub (Empliciti™)

Myelodysplastic/myeloproliferative disorders: Imatinib mesylate (Gleevec®), ruxolitinib phosphate (lakafi®)

Neuroblastoma: Dinuruximab (Unituxin ™)

Ovarian epithelial/fallopian tube/primary peritoneal cancers: Bevacizumab (Avastin®), olaparib (Lynparza™), rucaparib camsylate

(Rubraca™), niraparib tosylate monohydrate (Zejula™)

Pancreatic cancer: Erlotinib (Tarceva®), everolimus (Afinitor®), sunitinib (Sutent®)

Prostate cancer: Cabazitaxel (Jevtana®), enzalutamide (Xofigo®), abiraterone acetate (Zytiga®), radium 223 dichloride (Xofiqo®)

Skin cancer: Vismodegib (Erivedge®), sonidegib (Odomzo®), ipilimumab (Yervoy®), vemurafenib (Zelboraf®), trametinib (Mekinist®), dabrafenib (Tafinlar®), pembrolizumab (Keytruda®), nivolumab (Opdivo®), cobimetinib (Cotellic™), alitretinoin (Panretin®), avelumab (Bavencio®)

Soft tissue sarcoma: Pazopanib (Votrient®), Olaratumab (Lartruvo™), alitretinoin (Panretin®)

Systemic mastocytosis: lmatinib mesylate (Gleevec®), midostaurin (Rydapt®)
Thyroid cancer: Cabozantinib (Cometriq®), vandetanib (Caprelsa®), sorafenib (Nexavar®), lenvatinib mesylate (Lenvima®)

Where can I find information about clinical trials of targeted therapies?

Both FDA-approved and experimental targeted therapies for specific types of cancer are being studied in clinical trials. Descriptions of ongoing clinical trials that are testing types of targeted therapies in cancer patients can be accessed by searching NCI's list of cancer clinical trials. NCI's list of cancer clinical trials includes all NCI-supported clinical trials that are taking place across the United States and Canada and around the world. For information about other ways to search the list, see Help Finding NCI-Supported Clinical Trials.

Conclusion

Since the first identification of CSCs in leukemia, the important roles of CSCs in cancer progression, metastasis, and relapse as well as drug resistance have been increasingly recognized. Eradication of CSCs by targeting the key signaling pathways underlying CSC's stemness and function represents a promising approach in cancer treatment. In this review, we mainly sumnrarized the three critical evolutionarily conserved pathways (Wnt, HH, and Notch signaling) in CSCs and potential therapies targeting these pathways for cancer treatment. To date, numerous agents have been developed to specifically target each of these pathways for cancer treatments. Nevertheless, it has been recognized that the signaling pathways lnay interact with each other as a coordinated network to regulate CSC stemness and functions. Therefore, urderstanding the crosstalk among the signaling pathways in CSC regulation is critical for the development of therapies targeting CSCs [1-23].

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