Molecular Targeted Therapy

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Introduction

The basic of a cancer cell is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth (Fig 1): (1) self-sufficiency in growth signals, (2) insensitivity to growth-inhibitory (antigrowth) signals, (3) evasion of programmed cell death (apoptosis), (4) limitless replicative potential, (5) sustained angiogenesis, and (6) tissue invasion and metastasis.[1]

The rapid growth in knowledge of cancer biology has led to a more rational approach to therapeutic discovery through targeting of pathways and proteins that are essential for the survival of cancer cells. Discoveries in laboratories during the past decade have led to an improved understanding of specific biologic processes and signaling pathways important for survival, growth, and metastasis of neoplastic cells. (Fig 2)[1] The combination of this with technologic advances that allow sophisticated manipulation and analysis of nucleic acids and proteins, agents that target proteins or genes critical to the neoplastic process has been identified and further developed. A variety of compounds, including designed small molecules, monoclonal antibodies (mAbs), peptidomimetics, siRNA, antisense oligonucleotides, and expressed genes, and other molecularly targeted therapies are being evaluated for potential treatment of cancer, e.g., designed small molecules, and other molecularly targeted therapies in the treatment of cancer (Table 1). An increasing number of these agents have sufficient clinical activities from clinical trials to be important components of the current therapies for a number of different malignancies (Table 2).[2-6]

Targeted Therapy in Solid Tumor

In the treatment of cancer, we use drugs that lack selectivity for tumor cells. They are predominantly cytotoxic agents, lethal for tumors and normal tissues, with a narrow therapeutic index. Although they have measurably improved the treatment of many solid tumors and have cured some hematologic malignancies, and selected solid tumors but significant toxicity to normal tissues. The rapid growth in knowledge of cancer biology will allow a more rational approach to therapeutic discovery. This allows the targeting of pathways and proteins essential to the survival of cancer cells.

Recent studies of cancer biology have revealed a number of such pathways and proteins. Many of these are either overexpressed or in some way altered in cancer cells.

Possible targets include the overexpression of growth factor(EGFR) family, including the HER-2-neu tyrosine kinase; angiogenic pathways [e.g., vascular endothelial growth factor (VEGF) or platelet-derived growth factor (PDGF)-mediated angiogenesis] that provide a blood supply for the expanding tumor; antiapoptotic mechanisms that antagonize cell death, such as overexpression of Bcl-2 or decreased BAX expression; and enhanced activiity of intracellular signaling pathways that promote growth, impede apoptosis, or both. The most unique targets on cancer cells are mutation of genes, e.g., mutation of growth factor receptors include c-KIT in GIST7 and EGFR in NSCLC, both of which are small molecular inhibitors of their tyrosine kinase activity and have clinical benefit in quality of life and prolonging survival.[2-6]

Therapies that target tumor cells without affecting normal cells.

- Monoclonal antibodies that attach to tumor cells and either mark the cell for attack by the immune system, block specific transmembrane receptors, or deliver chemotherapeutic or radioactive drug.

Cetuximab (Erbitux) is a chimeric monoclonal antibody that binds the epidermal growth factor receptor (EGFR) in its extra-cellular domain. In preclinical studies activity was demonstrated in a wide range of human cancer cell lines.

Indications.

Monotherapy in patients intolerant to irinotecan
With irinotecan in patients refractory to irinotecan therapy.[8]

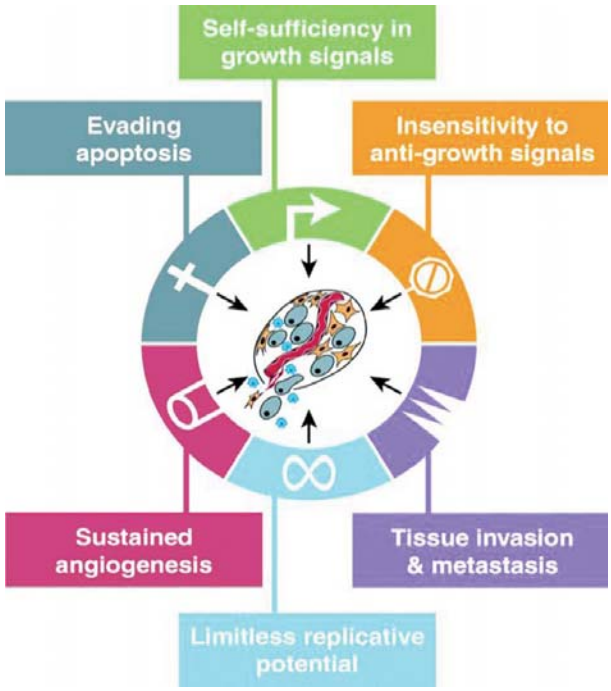

Fig 1. Acquired Cepabilities of Cencer[1]

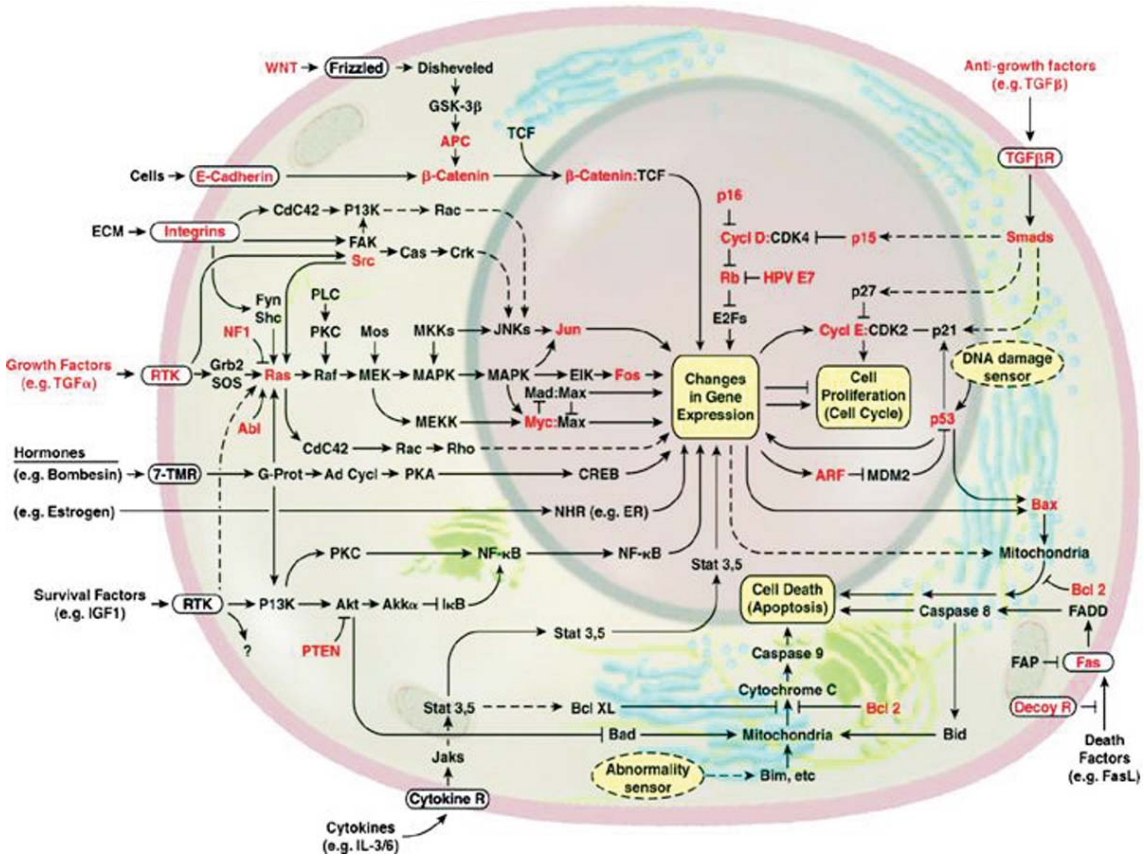

Fig 2. The Emergent Integrated Circuit of the Cell[1]

Bevacizumab (Avastin), a recombinant humanized monoclonal antibody, targets vascular endothelial growth factor (VEGF), which stimulates new vessel formation within the tumor.

Indications.

First-line treatment of patients with metastatic carcinoma of the colon and rectum (in combination with intravenous 5-fluorouracil-based chemotherapy)[9-11]

Trastuzumab (Herceptin), a humanized monoclonal antibody, inhibits cell growth by binding to the extra cellular part of the HER2 proteintyrosine kinase receptor, which is involved in the pathogenesis of breast and ovarian cancer. Trastuzumab induces antibody-dependent cellular toxicity by natural killer cells and monocytes against malignant cells.

Indications.

HER2-overexpressing metastatic breast cancer

Monotherapy in patients who have received 1 chemotherapy

With paclitaxel for chemotherapy-naive patients[12, 13]

- Drugs that inhibit signaling pathways for growth and proliferation within tumor cells:

Imatinib (Gleevec), a small-molecule drug, inhibits the intracellular part of three proteintyrosine kinases:

- Bcr-Abl, an abnormal fusion protein involved in the pathogenesis of chronic myelogenous leukemia. It is a product of the Philadelphia chromosome, a genetic abnormality present in patients with chronic myelogenous leukemia.
- c-kit (CD117), a receptor overexpressed in gastrointestinal stromal tumors (GIST)[7]
- Platelet-derived growth factor receptor alpha (involved in chronic myeloprolife-rative syndromes characterized by eosinophilia).

Indications.

Philadelphia chromosome-positive chronic-phase chronic myelogenous leukaemia (Ph+ CML) (newly diagnosed adults or pediatric patients after failure of stem cell tran-splant or interferon-α); Ph^+, Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-α[14]

c-KIT+ unresectable and/or metastatic gastrointestinal stromal tumor (GIST)[14,15]

Gefitinib (Iressa), a small-molecule drug, inhibits the intracellular portion of epider

TABLE 1. Molecularly targeted therapies.

Agent	Potential target(s)
Antisense oligonucleotides	RNA, DNA, proteins
Gene therapy	Neoplastic cells, immune mediator cells, and normal cells (to produce proteins)
Ribozymes	RNA and DNA in tumor cells
Monoclonal antibodies	Growth factor receptors, cell surface antigens, and other cellular proteins
Peptidomimetics/altered peptides	Growth factor receptors, cell surface antigens, extra- and intracellular proteins (e.g., enzymes and signal transduction molecules)
Small molecules	All of the above targets

TABLE 2. Approved Molecularly Targeted Agents.

Type of compound	Agents	Target	Indication
Uncoupled monoclonal antibodies	Alemtuzumab	CD52	B-CLL
	Bevacizumab (Avastin)	VEGF	Colorectal cancer
	Cetuximab (Erbitux)	EGFR	Colorectal cancer
	Trastuzumab (Herceptin)	Her-2	Breast cancer
	Rituximab (Mabthera)	CD20	B-cell lymphoma
Monoclonal antibodies coupled to radioactive or cytotoxic agents	Ibritumomab tiuxetan Y-90	CD20	B-cell lymphoma
	Tositumomab I-131	CD20	B-cell lymphoma
	Gemtuzimab ozogamicin	CD33	AML
Small molecules, Tyrosine kinase inhibitor (TKI)	Gefitinib (Iressa)	EGFR	NSCLC
	Imatinib (Gleevec)	BCR-ABL	CML
	Imatinib (Gleevec)	KIT	GIST
	Erlotinab (Tarceva)	EGFR	NSCLC
	Sunitinib (Sutent)	Multitargeted TKI,VEGFR, PDGFR, KIT, FLT3, RET	GIST, Kidney cancer

B-cell chronic lymphoid leukemia (B-CLL), acute myelogenous leukaemia (AML), chronic myelogenous leukaemia (CML), gastrointestinal stromal tumors (GIST), non-small cell lung cancer (NSCLC), vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2 or ErbB2), BCR - ABL fusion gene from t(9;22)(q34;q11) translocation, as an abnormal, small chromosome, named the 'Philadelphia chromosome', the c-kit proto-oncogene encodes a receptor tyrosine kinase (KIT) , tyrosine kinase inhibitor (TKI), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fetal liver (or Fms-like) tyrosine kinase 3 (FLT3), RET proto-oncogene (RET).

mal growth factor receptors (EGFR) which are involved in the activation of intracellular tyrosine kinase activity, which results in a cascade of intracellular signaling events, leading to cell proliferation, differen tiation, cell survival, angiogenesis, and invasion/me tastases. These receptors are overexpressed in non-small cell lung cancer (NSCLC) and other tumor types.[16, 17]

Indications.

Monotherapy for continued treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel chemotherapies[18]

Erlotinib (Traceva), a small-molecule drug, is a selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) as same as gefitinib.[17,19]

Indications.

Monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemo therapy regimen, and whose epidermal growth factor receptor (EGFR) expression status is positive or un known.[19, 20]

Sunitinib (Sutent), an oral multitargeted tyrosine kinase inhibitor (TKI) with antiangiogenic and antitu mor activities mediated by blockade of kinase activities associated with KIT, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth fac tor receptor (PDGFR), fetal liver (or Fms-like) tyrosine kinase 3 (FLT3), RET proto-oncogene (RET)[21-24]

Indications.

Monotherapy for advanced renal cell carcinoma[25-27]. Monotherapy for gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib (gleevec)[28, 29]

- Therapy to block expression of oncogenes and even perhaps replace missing or defective tumor-suppressor genes–the specific abnormalities that triggered the normal cell to become neoplastic in the first place and that allow the tumor cell to proliferate indefinitely. There are on going developments in basic science and transitional research.[2]

CONCLUSION

Increased knowledge of the mechanistic properties of malignant growth has facilitated the development of molecular-based therapies that can act on specific targets. These new agents offer a promising treatment option for patients with advanced cancer.

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