Curing “Incurable” Cancer

James D. Watson

Summary: Cancer cells are preferentially killed by anticancer agents because key signals for growth and cell division are “always on” as opposed to the alternative “on” and “off” signaling of normal cells. Too much of today’s anticancer drug discovery effort may go toward reversing genetically promoted “always on” signals. More effective anticancer drug targets may be found through use of RNAi technologies that pinpoint the key gene regulatory and metabolic weakness of the “always on” cancer cells. Cancer Discovery; 1(6):477-80. ©2011 AACR.

INTRODUCTION

Adult cells of higher organisms only grow and multiply when commanded to do so (1). The vast majority of adult human cells, however, are never destined to multiply. After they have been generated by their stem cell precursors, they become differentiated into a large multiple of nondividing cell types, such as the muscle cells which reversibly contract and expand, the kidney cells which move molecules through cell membranes, or the cells in our pancreas that synthesize vital digestive enzymes like pepsin and chymotrypsin. More recently, we have also learned in great detail about the many, many different growth initiating molecules that underlie embryologic development and/or repair the wear and tear of the adult gastrointestinal tract.

Cells in the prostate, for example, only divide after testosterone, made in the testes, binds to specific androgen receptors in the cytoplasm which then translocate to the nuclei and their DNA-containing chromosomes. After binding to specific sequences of the four bases, the androgen receptors trigger changes in gene expression and subsequent cell metabolism. Likewise, mammary cells require binding of the estrogen-hormone receptor complexes to their DNA before they can grow and later divide into progeny cells. Growth-provoking signals also can come from molecules made in adjacent cells. Skin epithelial cells require epidermal growth factor molecules (EGF) to bind to specific receptors on their cell surfaces.

The realization that all adult stem-like cells may require growth inputs from externally supplied molecules raised the possibility that many of the just discovered human onco-genes amplify the magnitude of normal growth signals. By the mid-1980s, using newly developed procedures for gene cloning, the molecular “signal transduction” pathways began to be worked out for the movement of growth signals from receptors at the cell surface to the turning on and off of gene expression in the nucleus (2). As they fell into place, precise targets for the development of a new class of anticancer drugs became obvious, leading to the establishment of the first biotech companies specifically focused on fighting cancer. Here on Long Island I helped found, in 1984, Oncogene Sciences (later OSI) to find drugs that blocked cell surface epidermal growth factor receptors. Hopefully, some, if not many, of the targeted drugs so found would work without also causing many of the highly debilitating, if not life-threatening, side effects of the then- and still-used anticancer drugs like doxorubicin, which work through damaging DNA molecules.

By now, there are at last in the clinic a growing number of targeted anticancer drug agents. Among them are the EGF receptor (EGFR)-binding drugs from OSI (Tarceva) and AstraZeneca (Iressa) which work best against the 10% of lung cancers that contain activating mutations in their tyrosine kinase EGFRs. However, with the exception of Gleevec’s deployment against chronic myelogenic leukemia (CML), whose growth is usually blocked as long as the drug is supplied, all too many of the new anti-growth therapies only briefly extend the lives of most cancer patients. The cancers they initially control later become tragically resistant to their inhibiting actions. For example, the drug Herceptin (Roche), given to breast cancer patients that have amplified numbers of the HER2 growth factor receptor, usually brings about remissions of months as opposed to years. How widely Herceptin will continue to be deployed may much depend on whether the money to buy it from Roche (more than $50,000 for a 1-year supply) comes from personal savings, employers’ funds, or possibly Medicare. Likewise, the cleverly designed new anti-BRAF drug from Plexxikon/Roche—just given the name Zelboraf—which selectively acts on the 50% of melanomas that possess mutated BRAF molecules, provides remissions of more than a year for only 20% of patients so treated. Furthermore, its not inconsiderable cost (also much more than $50,000 for a year’s treatment), when borne by individual patients, could much diminish the value of inheritances that would otherwise be passed on to the patient’s spouse or children.

Four major uncertainties thus face today’s world of anticancer therapy: (i) What is the nature of the changes (genetic or epigenetic) that lead to “incurable” drug resistance? (ii) Why are cancer cells more vulnerable to current chemotherapies than normal cells? (iii) Can we develop new drugs that specifically kill these incurable cancers? (iv) Will they become more affordable to today’s cash-strapped medical world? Until recently all these objectives have seemed beyond our reach. New science of the past year, however,
now makes me optimistic that the back of most incurable human cancers may be broken over the next 5 to 10 years. We, however, will likely only win soon if we put ourselves at risk by seemingly overpromising more success than many of my peers deem prudent to promise the public. Overpromising, however, could make the cancer research community stay at work on Saturdays and Sundays—not today’s way of life where scarce research funds create anxieties of running out of money and losing one’s salary.

NONGENETIC (EPIGENETIC) ORIGINS OF EPITHELIAL–MESENCHYMAL TRANSITIONS

Likely generating many, if not the vast majority, of chemotherapy-resistant solid cancers (e.g., colon, prostate, breast, lung) is the transformation of cancers originating in epithelial tissues (carcinomas) into much less organized sarcoma-like mesenchymal derivatives (3). Behind such epithelial–mesenchymal transitions (EMT) are epigenetic changes in gene expression similar to those which underlie development of fertilized eggs in highly differentiated multicellular organisms. The different set of growth factors that push mesenchymal cancers toward cell growth and cell division create an underlying metabolism that makes them much more resistant to cell-killing events than their epithelial cancer progenitors.

A major determinant of whether EMTs occur is the hypoxia-inducing gene-activating transcription factor (HIFs). When activated, either by the hypoxia found in the center of rapidly growing tumor cells or by signals from key cell growth-promoting molecules like mTOR, HIFs not only activates the very large number of genes needed to make the cellular building blocks for new cell growth but also induces the synthesis of the cMET cell surface receptor that plays a key role in inducing EMTs (4, 5).

One potential way to prevent epithelial cancers from becoming mesenchymal may be the deployment of drugs that specifically inhibit cMET function soon after epithelial cancers are diagnosed as opposed to restricting their use to later stage cancers (6). Unfortunately, U.S. Food and Drug Administration rules now too often prevent new drugs being used on cancer patients until the failure of drugs designed to work against early-stage cancers. By then, too many mesenchymal cancer cells have come into existence for anti-MET drugs to have much chance to exhibit their inherent anticancer potential.

MESENCHYMAL CANCER CELLS ARE NOT INHERENTLY LIFE THREATENING

Upon transition from their epithelial progenitors, mesenchymal cancer cells become inherently motile or capable of colonizing to other body locations, but they do not usually become life-threatening. In fact, just the opposite is often true. Underlying the seemingly inherent long dormancy of many newlycreated mesenchymal cancer cells is activation of transforming growth factor β (TGF-β) and its receptor TGFβR. Their binding promotes downstream synthesis of the SMAD4 transcription factor that in turn leads to the synthesis of cell cycle inhibiting proteins p15INK4b and p21 (7).

As long as SMAD4 molecules are being made, their respective cells are blocked from dividing. Only when the genes encoding SMAD4 or TGF-β become lost through mutations do prostate and pancreatic cancers, for example, become life threatening (8, 9). Dangerous melanoma, in contrast, comes into existence upon induction of the SKI transcription factor, which binds to SMAD4 DNA-binding sequences to prevent SMAD4 target gene activation. TGF-β-induced SMAD4 activity may be the major reason why early-stage cancer cells remain dormant long after they have metastasized to new locations. Only after inherently rare loss-of-function mutations occur within their respective tumor suppressor genes do they have the opportunity to proceed through cell division.

IL-6 CYTOKINES PROMOTE MESENCHYMAL CANCER CELL GROWTH AND DIVISION

We remain still much in the dark as to which molecules drive the growth and division of mesenchymal cells. The cell division-promoting cytokine interleukin 6 (IL-6) may be very important to creating these mesenchymal cancer stem cells. Its amounts in blood serum steadily increase in mesenchymal cancers of many origins (e.g., breast, lung, prostate, melanoma, and myeloma) as they transform into ever more aggressive forms (10). Binding of IL-6 molecules to their respective Janus activated kinase (JAK) cell surface receptors activates STAT3 transcription factors that in turn promote transcription of IL-6 genes. By so doing they create autocrine growth loops making their respective cancers partially if not totally independent of externally supplied growth drivers. How the first externally supplied IL-6 molecules come into existence remains unclear (11). One possibility is that the NF-κB transcription factor turns on transcription of the IL-6 gene. However, what brings about the earlier activation of NF-κB molecules is not yet clearly established. Conceivably, signal cascades generated from both EMT-generated TGF-β growth factors as well as inflammation-generated tumor necrosis factors (TNF) play this role.

That inflammation-induced cell growth and division promotes cancerous growth has long been known, the best known example being the generation of gastric cancers by inflammation resulting from growth of Helobacter pylori. Equally pertinent are the highly life-threatening qualities of “inflammatory cancers.” Massive infiltration of inflammatory cells, for example, makes it especially difficult to cure breast cancers. Epidemiologic findings that regular users of anti-inflammatory medicines like aspirin and ibuprofen have a 10% to 20% decreased incidence of cancer will be important to confirm.

EXCESSIVE GENERATION OF NEW CELLULAR BUILDING BLOCKS AND CELL ORGANELLES BY CANCER CELLS

Distinguishing cancer cells from normal cells is their inherently higher levels of glucose breakdown (glycolysis) and secretion of copious amounts of lactic acid even in the presence of oxygen (aerobic glycolysis)—a phenomenon first observed in the early 1920s by the great biochemist Otto Warburg, who received the Nobel Prize in 1931 for...
his insights about respiratory enzymes. Now we know that glycolytic breakdown of glucose and the glutaminolysis of the amino acid glutamine provide the cellular building blocks for the protein, nucleic acids, carbohydrates, and lipids needed for new cell growth (12). Cancer cells, in fact, break down sugar sources at even faster rates than their normal equivalents because one or more of their growth-promoting oncogenes are always on (13). To deal with the resulting excessive synthesis and prevent molecular suffocation due to accumulations of excessive biomass, cancer cells need to constantly self-digest and recycle many of their pre-existing proteins using proteosomes and cellular organelles through autophagy. Many incurable cancers may be helped by the development of new drugs that block one or more of the molecular steps of self-digestion (14).

Already cancers of antibody-forming plasma cells (multiple myeloma) are frequently being put into many-year remissions by treatment with the hugely successful drug Velcade (Millennium). Velcade is designed to inhibit proteosomes, the vital cellular protein aggregates that function to break down proteins when their specific presence is no longer needed, say, in passing from the G- to S-phase of the cell cycle. Blocking proteosome action preferentially puts antibody-producing cancerous plasma cells at risk likely because they are making more unfolded antibody chains than normal B lymphocytes can routinely process. The preferential killing of many cancer cell types by inhibitors of heat shock protein 90 (HSP90) stress-responding proteins likely also reflects the possession of larger numbers of unfolded nascent polypeptides in cancer cells than molecular chaperones can routinely guide into functional 3D conformations.

Whether the preferential susceptibility of cancer cells to a variety of untargeted cell growth-inhibiting agents (X-rays, DNA-damaging chemicals, oxidative, and metabolic stressors) arise out of their almost always “on” growth metabolism remains largely to be worked out. How cancer cells react to DNA-damaging agents is much influenced by whether they have functional p53 transcription factors. Loss of both p53 alleles greatly accelerates the ever faster growth of late-stage mesenchymal cancers. These cancers become much less able to repair damage done to their DNA by X-rays, UV irradiation, and DNA-damaging chemotherapeutic agents. Their resulting highly genetically rearranged chromosomes are marked by excessive copies of growth-promoting genes, like myc, cyclin D, and RAS, as well as loss of tumor suppressors like Rb that normally block unwanted growth and cell division.

**METABOLIC WEAKNESSES OF HIGHLY GLYCOLYTIC MESENCHYMAL CANCER CELLS**

Virtually all targeted anticancer drugs in use today have been developed to block the signal transduction pathways leading to the growth of epithelial cancers. However, this may not be the best approach. The increasingly uncontrolled constitutive growth-promoting metabolism of late-stage mesenchymal cancer cells leads them to produce even more cellular building blocks than their progenitor epithelial cancer cells. Exploiting their increasing addiction to glucose and glutamine consumption through the metabolic stress mediator AMP kinase therefore becomes a major way to stop them from becoming life threatening (15).

The best demonstration so far that such activated AMP kinase-generated metabolic stress selectively kills cancer cells comes from epidemiologic data showing that type 2 diabetestes patients who control their blood sugar levels by use of the AMP kinase-activated drug metformin have much lower incidence of cancer (16). Metformin most effectively kills those cancer cells which have lost both copies of the key regulatory p53 gene, whose normal functioning keeps sugar consumption at sustainable levels (17).

**ANTICANCER DRUGS THAT BLOCK VITAL CHROMOSOME FUNCTIONING MAY HAVE FEWER SIDE EFFECTS THAN DRUGS TARGETED TO STOP PROTEIN SYNTHESIS**

Anticancer drugs designed to block chromosome functioning may work much more effectively than targeted anticancer medicines that block the cytoplasmically located signaling pathways toward protein synthesis (cell growth). While a constant need to divide characterizes only a small fraction of our adult cells, active protein synthesis is a hallmark of almost all cellular existence except for that of the non-nucleated red blood cells. The nerve cells of our brains have to be constantly sending out new axons and dendrites to form ever-changing synaptic interconnections that underlie, for example, our abilities to perceive, memorize, and learn. Likewise the many, many cells involved in secreting vital digestive protein and steroid hormones can do so only when the throttles for the synthesis of new molecules are on. Therefore, no one should be surprised when anticancer drugs that work through blocking protein synthesis cause serious nausea, diarrhea, or fatigue.

Thanks to the completion of the 2003 Human Genome Project that provides us with the exact DNA sequences of all the some 22,000 human genes, powerful molecular inhibitors (RNAi) have been developed that selectively block the functioning of each human gene. They should let us identify, for example, those genes whose inhibition best blocks specific human cancers from dividing. The first epigenetically focused RNAi screen, done over the past year by Johannes Zuber and Chris Vakoc at the Cold Spring Harbor Laboratory, explored the chromosomal vulnerabilities of cell line and mouse xenograph models of untreatable human acute myelocytic leukemia (AML). Most unexpectedly, their experiments pinpointed the gene encoding the protein Bromodomain 4 (BRD4) as highly essential for uncontrolled cell division by AML cells. When they blocked its action using the BRD4-blocking drug JQ1, recently developed by James Bradner at the Dana-Farber Cancer Institute in Boston (18), they found rapidly dividing AML “blast” cells were converted into nondividing normal macrophages. Using JQ1 they further showed Brd4 makes their AML cell lines (in mouse models) “incurable” through expansion of the amounts of the key transcription factor myc, which in turn activates the synthesis of mRNA molecules for more than 1,000 different proteins needed to proceed through the cell cycle (19).

Clever prior experiments from Gerard Evans’ lab, now in Cambridge, England, show that myc is likely required for the
division of all stem cells, both normal and cancerous (20). No other cellular molecule can compensate for its loss. In its absence, normal stem cells remain dormant until myc is reintroduced. Cancer cells, in contrast, perhaps because of their myc-enhanced high glycolytic metabolism, preferentially die when myc is absent. JQ1 thus may have the potential not only to prevent leukemia cells from moving into cell division but also to block many other forms of cancer from growing and dividing.

Still to be determined is how many other molecules besides BRD4 function to turn on myc. Conceivably, many other genes have this capacity but so function at much lower rates and inherently lack BRD4’s capacity to generate late-stage, highly incurable mesenchymal cancers. The comparative strength of myc activators may determine their frequency as major drivers of cancer. It should not surprise us if JQ1 (which also acts on the BRD2 and BRD3 transcriptional activators) will be found to block the growth of many, but not all, forms of a given cancer.

Until JQ1 is used against human patients with AML and other deadly forms of cancer, we won’t know whether we have at last in our possession the long-sought-for miracle molecule that acts against a broad spectrum of different cancers without the life-diminishing side effects of most of today’s anticancer drugs. Fortunately, we shall not have to bite our fingernails for unbearably long intervals. Within 18 months, we likely will know if we at last have found the way to win big. Time cannot move fast enough!

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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