Musings

Musings on genome medicine: cancer genetics and the promise of effective treatment

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Abstract

Cancer is the most common acquired genetic disease. Great progress has been made in documenting the genetic abnormalities that cause the disease, and in the future each tumor will be subjected to genetic analysis and the appropriate combination of drugs selected. Although there are serious technological and cost hurdles to surmount and resistance and continued mutation will be a constant problem, the way is clear to rational therapy.

The explosion in the knowledge of cancer genetics of the past 25 years has totally changed our approach to cancer treatment. Indeed, we are in the midst of a cancer treatment revolution [1]. But, as is true of many political and cultural revolutions, the pace of progress is maddeningly ponderous. Although recent relaxations of the grips of smoking and hormone replacement therapy has led to a welcome decline in cancer incidence [2], millions more lives will be lost before we truly understand or have the tools to provide effective therapy for this vastly complex group of diseases.

Despite the long road ahead, investigators, clinicians and patients share a mounting confidence that new therapeutic research will ultimately be successful. Through oncogenetics, we will be able to document the drivers of an individual cancer and delineate the gain-of-function mutations that give rise to growth-promoting proteins that in turn induce oncogene 'addiction', in which a cancer is dependent on such proteins. We will also determine the loss-of-function mutations that deprive cancer cells of the proteins that direct DNA repair and/or provide directions to the cell death pathway. Armed with such oncogenetic data, we will match the validated mutations of a particular cancer to an appropriate and scientifically determined targeted drug array. This great challenge, one akin to President Kennedy's thrust to the moon, is definitely possible. Here, we provide the background to our optimism and also describe some of the roadblocks that obstruct the path of progress.

Modern treatment of invasive cancers that have extended beyond the reach of the surgeon's knife or the radiation therapist's beam began in the post World War II era when Sidney Farber and his colleagues introduced aminopterin to induce remissions in childhood leukemia [3]. Farber was committed to sequential application of single agents and urged an extensive public and private antibiotic and anti-cancer drug screening program to produce many active compounds that had in common the induction of injuries to cell DNA or the process of cell division. These were eventually used in various combinations with the intent of achieving selective toxicity and minimizing resistance. The results were variable. After 50 years of almost entirely empirical clinical trials, combination chemotherapy moved the prognosis of standard childhood leukemia from invariably fatal to an 85% cure rate [4]. The outcome of systemic Hodgkin's Disease was similarly improved. Clear-cut benefit was established in breast, head and neck, ovarian, testicular and colon cancer. But very little progress was made in lung, prostate, liver, pancreas or brain cancer,

and the toxicities of the treatments remain considerable - normal cells as well as cancer cells are badly injured in the process. Although surgery, radiation therapy and combination chemotherapy have made an impact on the disease, early and late side effects are significant. Towards the end of the 20th century it became clear that the efficacy of this 'carpet-bombing' treatment of cancer had reached a plateau.

During this period of trial and error some critically important concepts of cancer pathophysiology have been realized. Chromosomes in the leukemias and lymphomas may appear normal but frequently show translocations and deletions that provide clues to the relatively few genes that are responsible for such tumors [4]. In contrast, the chromosomes in epithelial cancer cells are almost always broadly and heavily damaged [5]. The chromosome wreckage includes massive deletions, amplifications and rearrangements, as well as point mutations and translocations, and can be observed in very early stages of the growth of such tumors. The latter observation suggests that several mutated genes in an individual cancer may be responsible for the malignant state and that many more are mere accidents of the chromosome breakage. The art of oncogenetics lies in validating the relatively few significant mutations and differentiating them from the many innocuous byproducts of the chromosome breakdown that characterizes the epithelial cancer process. Put simply, the epithelial cancer problem can be understood and effectively treated only by documentation of the truly oncogenic results of widespread DNA damage. This demonstrates the critical importance of advances in the detection of cancer-causing genes.

The role of cancer genetics as a discipline that would probably lead to more effective targeted treatment was highlighted by the discovery of a gain-of-function *Abl kinase* gene that produced hyperactive Abl kinase, a unique driver of early stage chronic myelogenous leukemia [6,7]. In fact the successful interruption of unbridled Abl kinase activity by imatinib ushered in a new era of 'smart drug' treatment of cancer [8]. In this new era, three major paths of progress have been and continue to be explored. The first has used patient-derived cancers, transgenic mice [9] and transfected cells [10], DNA and RNA (including microRNA) array technology [11] and gene sequencing [12] to establish potential genetic drivers of the initiation and maintenance of cancer cell growth. The second approach has focused on the failure of human and murine cancer cells either to repair their damaged DNA [13] or, without DNA repair, to plunge fatally into a metabolic death pathway [14]. Both failures contribute to the malignant process, particularly in the common human epithelial cancers and also in certain lymphomas.

A third and more recent approach has examined the organ environment of cancer and has revealed that the stromal fibroblasts surrounding cancer cells, such as ductal carcinomas, exude signals that break down the myoepithelial cell barrier that would otherwise confine the cancer cells to the duct [15-17]. Furthermore, certain cancers, such as neurofibromas that arise as a result of homozygous loss-of-function mutations of a tumor suppressor gene (*NF1*), do not become actual tumors unless their surrounding stromal cells lack one of the two copies of the gene [18]. Finally, some cancers induce supporting cells to maintain cancer cell viability. This effect includes but is not limited to vascular endothelial cells [19].

In all three of these areas of oncogenetic research, drugs and antibodies have been sought that would either block gain-of-function proteins or replace key loss-of-function proteins. A considerable effort has also been expended to produce murine models of epithelial cancers so as to hasten the development of effective therapies [20]. While this extensive basic research has been in progress, clinical scientists have been exploring the many 'smart drugs' that have come off the assembly lines of pharmaceutical companies. What have been the results of all of this effort?

Among the first waves of research have been discoveries of the genetic drivers of common and uncommon cancers. Breast cancers, whether acquired or (rarely) inherited, are prime examples. Despite vast chromosome damage and multiple mutations, most breast cancers are largely maintained by overexpression or possibly (and contested) amplification of the estrogen and progesterone receptor genes [21]. Simple estrogen receptor blockade or inhibition of estrogen synthesis combined with limited surgery and radiation therapy and ordinary combination chemotherapy can cure up to 80% of these cancers if they are diagnosed before widespread disease has occurred [22]. In approximately 20% of cases a different mutation is responsible for the malignant state. In those less common cases the cause is amplification of *Her2-neu*, a receptor kinase gene that expresses a subtype of an epidermal growth factor receptor [23]. Such *Her2-neu*-positive cases have, until recently, been burdened by a very poor prognosis. However, recent clinical studies have demonstrated that early infusions of traztuzumab, a monoclonal antibody directed against the receptor, combined with standard treatment markedly improves the outlook for these heretofore unfortunate patients [24]. The third major subtype of breast cancer, representing about 15% of cases, includes the so-called basal-like or triple-negative tumors that lack estrogen and progesterone receptors and *Her2-neu* and have not been amenable to targeted therapy. Recently, however, advantage has been taken of the resemblance of these tumors to those of the rare *BRCA1* mutation carriers who have a high rate of inherited breast cancer. *BRCA1* and *BRCA2* are DNA repair genes; they thus provide protection from DNA cross-linking agents, such as radiation or cisplatinum. Basal-like tumors are therefore sensitive to cisplatinum and poly ADP ribose polymerase (PARP) inhibitors, an excellent example of how inquiries into cancer genetics improve cancer therapy.

Diffuse gastrointestinal stromal tumor, a rare and uniformly fatal sarcoma that, in its advanced stages, also shows severe chromosomal damage, can be obliterated by imatinib [25]. Resistance generally (but not always) occurs when the drug is used as a single agent, but the dramatic effect of imatinib proves that such tumors become dependent on or addicted to mutated tyrosine kinases (in this case Kit or platelet derived growth factor receptor). The dramatic therapeutic results provide a remarkable example of the value of a single drug that can interrupt more than one of the gain-of-function proteins that drive such tumors [26]. Given that there are over 500 protein kinases in the human 'kinome', major efforts are now in place to define their roles in the hundreds of fatal cancers. Slowly but surely, incriminating evidence is being gathered that implicates previously unsuspected kinase mutations in various cancers. Neuroblastoma is an excellent recent example [27].

In addition to kinase drivers, the genes of other growth promoters, including transcription factors such as Myc or signaling proteins such as Wnt, have been shown to be mutated or amplified in many different cancers [28]. They surely have an important role in the maintenance of unbridled growth. Indeed, mutations of kinases seem to be relatively uncommon causes of cancer, although they are the subjects of recent excitement.

Finally, loss-of-function mutations of DNA repair genes prevent the repair of cancer-inducing genes [29], and the frequently observed loss or inactivation of genes such as *p53* and *MDM2* reduces the capacity of injured cancer cells to quit the cellular scene by means of apoptosis [30]. This leads to cancer-cell immortality and failure of cancer chemotherapy and radiotherapy to achieve cancer cell death. In an entirely novel approach to drug development, peptides 'stapled' by fatty acids have been used as effective experimental drugs that replace such missing proteins [31].

As DNA sequencing and array technology advances, investigators are churning out vast amounts of genetic information about common cancers, such as colon, breast, prostate, pancreas, lung and glioblastoma [32-36], and about unusual cancers, such as mesothelioma [37]. Recently, the entire DNA sequence of a single case of acute myelogenous leukemia that had a normal karyotype was published. In addition to two previously described genetic abnormalities, six previously unappreciated mutations were observed [38]. However, much of the data derived from such massive efforts may be misleading. It is likely that only a few of the detected DNA variations that emerge from complete DNA sequencing will actually prove to be responsible for the tumors. The immense task is to sort through them and define them and then develop the drugs to either block or replace them. Then we must face the pernicious problems of genetic or epigenetic mutational heterogeneity among the cells in a single tumor and of continued mutation. If we have the appropriate drugs, can we kill the cancer cells before they mutate again to develop new drivers that were not present before our new therapy was launched? We need to develop the tools that will allow us to define tumor genetic and epigenetic heterogeneity.

Even when we solve those diagnostic problems (and we will), we and our patients face yet another barrier. It is already very clear that the new 'smart drug' era does not imply that we will be successful very often with single agents. Cancer cells with extra-labile DNA will mutate to circumvent smart drugs very easily. This means that we must treat patients with combinations of drugs that block multiple metabolic pathways. Toxicity may become a very severe problem as we force patients down that route.

Despite all these caveats, excitement is in the air. We are on the verge of understanding the biology of cancer, and with that understanding will come the drugs that will help us to beat it down. We may not actually cure all or even many of our previously unmanageable patients, but we will convert such cancers from killers to chronic smoldering illnesses that can be endured. Our goal will be to provide cancer sufferers with a fulfilling life. This objective has been achieved in many cases of AIDS. We will surely get at least that far for patients with cancer. It will take years of hard work, but we owe that commitment to the cancer patients who rely on us for a better future. A thorough understanding of oncogenetics will show us the way.

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