radically) has been constant despite to this change in surgery and the use of radiotherapy. Therefore, the next step will be to take into account the risk of distant metastases. Based upon preoperative staging upfront chemotherapy might be a solution.

Pezcoller Foundation/FECS recognition for Contribution to Oncology

8 Pezcoller/FECS Award

Functional genetic approaches to cancer

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The quantum leap forward in our understanding of the molecular basis of cancer over the past two decades has not yet been accompanied in a comparable increase in our ability to diagnose or treat cancer. In this lecture I will illustrate how we can exploit the power of genetics and genomics to greatly improve the diagnosis of cancer and develop new and far more powerful classes of anti cancer drugs.

Better diagnostics: Cancer is a disease that results from changes in cellular gene expression. As the behavior of cancer cells is determined by the expression of their genome, the pattern of gene expression may reveal many traits of individual cancers, including responses to anti-cancer therapies and propensity to form distant metastases. In the past, numerous clinical studies have correlated expression levels of individual genes with disease outcome. In general, the results of these studies have been disappointing. This indicates that individual genes have only limited predictive power and points to the need for a multi-gene-based approach. We have used DNA micro-array technology to obtain detailed insights into the behavior of tumors. By analyzing patterns of gene expression in a series of breast cancer of varying aggressiveness, we were able to identify a 70-gene signature that predicts the development of distant metastases in breast cancer. This gene signature has been developed into the first micro-array based diagnostic test for cancer. The availability of clinically-useful and validated gene signatures will help breast cancer patients in making difficult therapy choices.

Our current efforts in this area are focused on the identification of gene expression profiles that predict responses to new generations of anti-cancer drugs, the targeted therapeutics. These drugs often target specific molecules that are hyper-active in cancer (examples are the HER2/NEU receptor in breast cancer, the BCR-ABL kinase in chronic myeloid leukemia and the EGF receptor in lung and colorectal cancer). These drugs are often very effective and have very few unpleasant side effects other than their steep price. It is widely believed that in the next 5 to 10 years the clinical application of these new targeted therapeutic agents will personalize, and thereby revolutionize, the care for cancer patients The price issue is a serious one, as it becomes increasingly clear that there is a limit on the amount of money society can spend on cancer drugs. The development of diagnostics to identify those patients that benefit most from expensive targeted therapeutics may help solve this societal dilemma.

Better therapeutics: One of the major remaining deficits in our understanding of the human genome is that information regarding gene function is available for only one quarter of the approximately 30,000 genes. Many of these hitherto anonymous genes are potential targets for the development of new anti-cancer drugs. My laboratory has developed functional genetic approaches to obtain information regarding gene function using high-throughput screens. We have developed both gain-of-function genetic screens and loss-of-function genetic screens to carry out large-scale genetic screens in mammalian cells. We focus on the central growth-regulatory pathways that are most frequently deregulated in cancer.

One attractive new opportunity provided by the new genetic tools available to cancer geneticists is that it allows us to identify completely new and innovative classes of anti cancer drugs. One concept that was formulated as early as 1997 by Hartwell and Friend is that of genotype-specific drug targets, *i.e.* targets whose inhibition is only toxic to cells carrying a defined (cancer-specific) genetic lesion. In theory, such drugs should be far more selective for cancer cells than the current generation of broadly-acting cytotoxic drugs. Unfortunately, this concept of "synthetic lethal" interactions has remained a subject about which more reviews have been written than solid data published. Nevertheless, given the frequent occurrence of synthetic lethal interactions in yeast, such interactions will sooner of later also be found in mammalian cells. I will discuss our own efforts in identification of new classes of drug targets using large-scale RNA interference screens in mammalian cells.

Young Oncologists session
How to select a target for chemoprevention? Illustration based on mTOR pathway inhibition

9 INVITED

mTOR pathway and cancer: general concepts

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Target of Rapamycin (TOR) is a serine/threonine kinase whose function is conserved from yeast to metazoans. Depending on nutrient availability, TOR regulates cell number and size, by promoting cell cycle progression, cell survival and anabolic pathways. In mammals, the insulin and insulin-like growth factors (IGFs) also participates in TOR regulation via the Insulin Receptor Substrates (IRS), phosphatidyl inositide 3 kinase (PI3K) and the small GTPase Rheb. Mammalian TOR (mTOR) exists in two complexes. The first includes the raptor protein, is inhibited by the macrolide antibiotic rapamycin, and phosphorylates the S6 kinase (S6K) and eIF4E-binding protein (4EBP) families. The second complex includes the rictor protein, is insensitive to rapamycin and phosphorylates the Akt (PKB) kinases, as well as other kinases of the AGC family. By using mouse genetics and rapamycin, our group is addressing how pathophysiological growth and proliferation are controlled by this pathway. We show that muscle cell size and cell number are regulated by separate branches of the mTOR pathway and that S6K1 is selectively required for size control. Since tumours having deregulated activity of the PI3K/Akt pathway are often extremely sensitive to rapamycin, our group is also addressing the role of S6K1 in tumorigenesis. We have characterised a mouse model of insulinoma by overexpressing the oncogenic form of Akt under the rat insulin promoter (RIP-MyrAkt1). These mice develop tumors, starting at four months of age and progressing to 60% of incidence and decreased viability after ten months. Strikingly, the S6K1 deletion is sufficient to block pancreatic beta cell tumorigenesis. In conclusion, we propose S6K1 may serve as a mTOR effector promoting growth and tumorigenesis.

10 INVITED

Rapamycin analogs in cancer therapy

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mTOR has been shown to be a key kinase acting downstream of the activation of the phosphatidylinositol 3 kinase (PI3K). In humans, mTOR is a nutrient sensing protein acting as a master switch of cellular catabolism and anabolism, signaling cells to multiple critical effects including cell growth, proliferation and survival. Rapamycin and its analogs (CCI-779, RAD001 or everolimus, and AP23576) are macrolides that block mTOR. Initially, these compounds were developed as immunosuppressive drugs. Interestingly, rapamycin and its derivatives have been shown to inhibit the growth of several human cancer cell lines in preclinical models. Based on this preclinical activity, rapamycin and its analogs are being clinically developed as anticancer drugs. These compounds have been evaluated in both continuous and intermittent schedules. They have a favorable safety profile with skin rash as the most frequent side-effect, the dose-limiting toxicities being mainly thrombocytopenia, mucositis, and asthenia. Evidence of long-lasting antitumour activity has been reported in patients with breast cancer, renal cell carcinoma and colon cancer. This clinical activity has not been shown to be dose- or schedule-dependant. Surrogate downstream and upstream molecular markers are being used to monitor the biological effects of rapamycin derivatives in order to determine the optimal biological dose with these compounds, although that preliminary evidence suggest that this approach might be insufficient to predict response. The molecular characterization of the activation status of m-TOR related signaling pathways as well as the mutational status of some selected genes might provide critical information to identify the population that might be more sensitive to these compounds. Rapamycin analogs are also being developed in combination with hormone agents, chemotherapy and other targeted agents. Some preclinical studies have elegantly defined opportunities for these combinations with the simultaneous inhibition of multiple signaling pathways thereby preventing resistance induced by intracellular crosstalk and signaling redundancies. In summary, m-TOR inhibitors are agents with anti-cancer activity and a favorable safety profile. Through a better understanding of the m-TOR-related signaling pathways and the precise knowledge of the potential synergistic or additive interactions with other drugs, the clinical development of rapamycin analogs will continue to expand.