Molecular Medicine in Cancer Research

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1. INTRODUCTION: CANCER AND MOLECULAR MEDICINE

Cancer has become a big threat to human beings globally.[1] Total cancer cases are likely to go up from 979,786 in the year 2010 to 1,148,757 in the year 2020.[2] Every year, nearly 10 million people are being diagnosed with cancer out of which about 6 million die per year.[3] The most effective way to deal with cancer would be to prevent development of the disease. A second-best, but still effective, alternative would be to reliably detect early premalignant stages of tumor development that can be easily treated. [4]

Molecular medicine is a broad field, where physical, chemical, biological and medical techniques are used to describe molecular structures and mechanisms, identify fundamental molecular and genetic errors of disease including cancer, and to develop molecular interventions to correct them. [5] Some of the key approaches are briefly discussed below.

2. NANOTECHNOLOGY

Certain nanoparticles (NP) can be designed to absorb preferentially certain wavelength of radiation and if they enter in the cancerous cells, they will burn them. Nanotechnology can be used to create therapeutic agents that target specific cells and deliver toxin to kill them. The NP will circulate through the body, detect cancer associated molecular changes, assist with imaging, release a therapeutic agent and then monitor the effectiveness of the intervention.[6] Nanotechnology has the potential to revolutionize cancer diagnosis and therapy.

Advances in protein engineering and materials science have contributed to novel nanoscale targeting approaches that may bring new hope to cancer patients. Several therapeutic nano carriers have been approved for clinical use. However, to date, there are only a few clinically approved nano carriers that incorporate molecules to selectively bind and target cancer cells. [7]

3. MOLECULAR ANALYSIS OF ONCOGENES AND ANTI-ONCOGENES

Molecular analysis of the oncogenes and anti-oncogenes/ tumor suppressor genes involved in particular types of tumors has the potential of providing information that is useful in the diagnosis of cancer and in monitoring the effects of treatment. The translocation of *abl* in chronic myelogenous leukemia (CML) is a good example. Translocation results in the fusion of *abl* with the *bcr* gene, leading to expression of the Bcr/Abl oncogenesprotein. The polymerase chain reaction provides a sensitive method of detecting the recombinant *bcr/abl* oncogene in leukemic cells and is therefore used to monitor the response of patients to treatment. In other cases, the detection of mutations in specific oncogenes or tumor suppressor genes may provide information pertinent to choosing between different therapeutic options. For example, amplification of N-*myc* in neuroblastomas and *erb*B-2 in breast and ovarian carcinomas predicts rapid disease progression. Therefore, it might be appropriate to treat patients with such amplified oncogenes more aggressively. Because of the role of p53 in apoptosis induced by DNA damage, analysis of *p53* mutations may help predict the response of tumors to radiation and chemotherapy.[4]Of the mutated genes in cancer, driver gene with oncogene addiction is strongly involved in the development and progression of cancer and dependent on tumor survival. More recently, new driver genes such as RET fusion, ROS1 rearrangement, BRAF mutations, HER2 insertions, PIK3CA mutations, FGFR1 amplifications, and DDR2 mutations were also identified and these driver mutations are expected as a target for new therapeutic medicines.[8]

4. GENE THERAPY

Adenovirus vector (AV) is the most commonly studied and most widely used system in cancer gene therapy. It is of particular use for cancer gene therapy applications, where temporary gene expression is acceptable or even beneficial. There are several serotypes, but the currently employed AVs in clinical trials are mostly based on serotype. These vectors scan replicate highly and have demonstrated efficient gene transfer into various types of cancer cells. However, even this system suffers from several deficiencies: First, the vectors currently have to be injected intra tumourally to elicit an effect. This is far from ideal as many tumors are inaccessible and spread to other areas of the body making them difficult to detect and treat. Second, because of the heterogeneity within a tumor, the vector does not efficiently enter and spread to sufficient numbers of tumor cells. Third, hypoxia, a prevalent characteristic feature of most solid tumors, reduces the ability of the viral vector to function and decrease viral gene expression and production. Consequently, a proportion of the tumor mass is left unaffected and capable of re-growing. Fourth, pre-existing immunity pose a problem for the efficacy of viral vectors. Therefore, there have rarely been any cures with the use of the system on strated efficient gene transfer into various types of cancer cells.[9]

5. MICRO RNA (MIRNA)

Many miRNAs have been suggested as playing a key role in cancer owing to their location and expression profiles. The first experimental evidence that miRNAs are involved in mammalian carcinogenesis was reported in CLL, the most common form of adult leukaemia in the Western world.[12] Compared with other RNA inhibition techniques (such as antisenseoligonucleotides (ASOs), ribozymes, and siRNAs), the major advantage of using miRNAs to treat cancer patients is that a specific miRNA targets several genes involved in the same pathway. For example, among the components of themiR-15a/16-1 signature in CLL, a disease in which the main altered cell program is apoptosis, we observed significant enrichment in cancer genes (such as MCL1, BCL2, ETS1, andPDCD6IP) that directly or indirectly affect apoptosis and the cell cycle. Therefore, by targeting miRNAs, a more effective functional restoration of the abnormal pathway can be achieved than can be achieved with the usual one agent, one-target effect characteristic of all other RNA inhibition agents. [10]

6. STEM CELL

The cancer stem cell hypothesis posits that cancer stem cells are a minority population of self-renewing cancer cells that fuel tumor growth and remain in patients after conventional therapy has been completed. The hypothesis predicts that effective tumor eradication will require obtaining agents that can target cancer stem cells while sparing normal stem cells. Experimental evidence in human AML suggests that, compared with the bulk population of leukemic blasts, the leukaemia stem cells are relatively resistant to conventional chemotherapeutic agents. Although it has been speculated in solid tumors that conventional agents kill the non tumorigenic cancer cells while sparing the cancer stem cells, this has not been proven. There are other models of drug resistance consistent with the existence of cancer stem cells that could explain relapse, including the classic view of mutation and selection. The moving target nature of cancer stem cells may present a challenge in the clinic. To achieve effective implementation of new therapies, physicians will require methods of determining the type (or types) of cancer stem cells present in a given patient's tumor. Work involving 150 CML patient peripheral blood and bone marrow samples is encouraging in that patients in blast crisis all exhibited an expansion of the granulocyte-macrophage progenitor population, which included the fraction displaying stem cell properties. Therefore, it seems reasonable to expect that tumors sharing a similar pathology may also share common features in their cancer stem cell populations, which would facilitate diagnosis and the application of appropriate treatments. It is important that agents directed against cancer stem cells discriminate between cancer stem cells and normal stem cells. This will require identification of realistic drug targets unique to cancer stem cells. The identification of such targets and the

development of anticancer agents will require a fuller understanding of normal stem cell biology as well as the genetics and epigenetic of tumor progression. There is some indication that such an approach can be successful.[11]

7. MONOCLONAL ANTIBODIES

A major milestone in the rational development of drugs targeted against specific oncogenes was reached in 1998, when the FDA approved Herceptin for treatment of metastatic breast cancer. Herceptin is a monoclonal antibody against the ErbB-2 oncogeneprotein, which is over expressed in about 30% of breast cancers as a result of amplification of the erbB-2 gene. It was first found that an antibody against the extracellular domain of ErbB-2 (a receptor protein-tyrosine kinase) inhibited the proliferation of tumor cells in which ErbB-2 was over expressed. These results led to the development and clinical testing of Herceptin, which was found to significantly reduce tumor growth and prolong patient survival in clinical trials involving over 600 women with metastatic breast cancers that over expressed the ErbB-2 protein. Based on these results, Herceptin became the first drug developed against a specific oncogene to achieve FDA approval for clinical use in cancer treatment. [4]Specific monoclonal antibodies targeted to cell surface receptors and specific agents that inactivate kinase in growth-promoting pathways, have improved the response rate in cancer and reduced side effects of anticancer treatment but has not yet resulted in cure of the majority of patients with metastatic disease.[12]

8. ANTI ANGIOGENESIS

Tumor cells secrete a number of growth factors that stimulate the proliferation of capillary endothelial cells, resulting in the outgrowth of new capillaries into the tumor. The importance of angiogenesis was first recognized by Judah Folkman in 1971, and continuing research by Folkman and his colleagues has led to the development of new drugs (endostatin and angiostatin) that inhibit angiogenesis by blocking the proliferation of endothelial cells. Because these drugs act specifically to inhibit the formation of new blood vessels, they are much less toxic to normal cells than standard anticancer agents. Angiogenesis inhibitors have shown very promising results in animal tests, and are currently being tested in clinical trials to evaluate their effectiveness against human cancers. [8]

9. CONCLUSIONS AND FUTURE PERSPECTIVES

Molecular medicine has brought great excitement and promise to the concept of cancer diagnostics and therapy. A better understanding of the molecular pathology of cancer and feed-back from current diagnostic/treatment modalities shall foster improved applications of molecular medicine in oncology in future.

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