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A SILENT CRISIS: RECENT DRUG DISCOVERY IN CANCER RESEARCH

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ABSTRACT

This article represents the recent drug discovery in cancer research. Cancer is a term which describes a group of perhaps 120 different diseases which share some broad similarities. The body is made up of hundreds of millions of living cells. Normal body cells grow, divide into new cells, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells. Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells can also invade (grow into) other tissues, something that normal cells cannot do. Growing out of control and invading other tissues are what makes a cell a cancer cell. With the help of recent development in cancer research that will made easy to treat all types of cancer.

Key words: Cancer; DNA; Mutation; Chemotherapy; Cyto-toxic drug; Radiation therapy; Hormonal therapy; Biological therapy; RNAi technology etc.

INTRODUCTION

The body is made up of hundreds of millions of living cells. Normal body cells grow, divide into new cells, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells. Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells can also invade (grow into) other tissues, something that normal cells cannot do. Growing out of control and invading other tissues are what makes a cell a cancer cell. Cells become cancer cells because of damage to DNA. DNA is in every cell and directs all its actions. In a normal cell, when DNA gets damaged the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, but the cell doesn't die like it should. Instead, this cell goes on making new cells that the body does not need. These new cells will all have the same damaged DNA as the first cell does [1].

The Origin of Cancer

Cancer is a term which describes a group of perhaps 120 different diseases which share some broad similarities. In these diseases, a single cell begins to divide uncontrollably forming a tumor, and eventually bits of this tumor break off and form new tumors (this is known as metastasis). Normal cells do not divide in this fashion, being kept under tight control by a number of different biological mechanisms that are still being explored. We do know that cell division is controlled by a relatively small group of enzymes. Some of these operate to form a communication network, relaying growth signals from the surface of the cell to its DNA and telling it when to begin dividing. Others work as a surveillance team, preventing a

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cell with damaged DNA from reproducing by first repairing the damage or by instructing it to die. However, sometimes the damage (mutation) occurs in the DNA that codes for these enzymes, so that they are themselves defective. Such a cell will divide uncontrollably, and produce daughter cells that do the same. A human cell contains approximately 100 000 genes, of which about 50 are known as proto-oncogenes. Many of these codes for the enzymes that make up the communication and surveillance systems described above. If a cell accumulates critical mutations in five or six of these proto-oncogene, the resulting multiple but subtle changes are likely to result in a fully malignant cell, capable of forming a tumor [2].

Treatment

Chemotherapy

The word chemotherapy means the use of any drug (such as aspirin or penicillin) to treat any disease, but to most people chemotherapy refers to drugs used for cancer treatment. It's often shortened to "chemo." Two other medical terms used to describe cancer chemotherapy are antineoplastic (meaning anti-cancer) therapy and cytotoxic (cellkilling) therapy [3].

Goal of chemotherapy

There are 3 possible goals for chemotherapy treatment:

Cure

If possible, chemotherapy is used to cure the cancer, meaning that the cancer disappears and does not return. However, most doctors do not use the word "cure" except as a possibility or intention. When giving treatment that has a chance of curing a person's cancer, the doctor may describe it as treatment with *curative intent*. But there are no guarantees, and though cure may be the goal, it doesn't always work out that way. It often takes many years to know if a person's cancer is actually cured.

Control

If cure is not possible, the goal may be to control the disease — to shrink any cancerous tumors and/or stop the cancer from growing and spreading. This can help someone with cancer feel better and possibly live longer. In many cases, the cancer does not completely go away but is controlled and managed as a chronic disease, much like heart disease or diabetes. In other cases, the cancer may even seem to have gone away for a while, but it's expected to come back.

Palliation

When the cancer is at an advanced stage, chemotherapy drugs may be used to relieve symptoms caused by the cancer. When the only goal of a certain treatment is to improve the quality of life but not treat the disease itself, it's called palliative treatment or palliation [4].

Chemo that's given with other treatments

Sometimes, chemotherapy is the only treatment used. In other cases, chemotherapy may be given along with other treatments. It may be used as adjuvant therapy or neoadjuvant therapy.

Adjuvant chemotherapy

After surgery to remove the cancer, there may still be some cancer cells left behind that cannot be seen. When drugs are used to kill those unseen cancer cells, it's called adjuvant chemotherapy. Adjuvant treatment can also be given after radiation. An example of this would be adjuvant hormone therapy after radiation for prostate cancer.

Neoadjuvant chemotherapy

Chemotherapy can be given before the main cancer treatment (such as surgery or radiation). Giving chemotherapy first can shrink a large cancerous tumor, making it easier to remove with surgery. Shrinking the tumor may also allow it to be treated more easily with radiation. Neoadjuvant chemotherapy also can kill small deposits of cancer cells that cannot be seen on scans or x-rays [5].

Cytotoxic (cell-killing) drugs

The majority of drugs used for the treatment of cancer today are cytotoxic (cell-killing) drugs that work by interfering in some way with the operation of the cell's DNA. Cytotoxic drugs have the potential to be very harmful to the body unless they are very specific to cancer cells - something difficult to achieve because the modifications that change a healthy cell into a cancerous one are very subtle. A major challenge is to design new drugs that will be more selective for cancer cells, and thus have lesser side effects. Initially the specificity of drugs was worked out simply by testing on animals, but now it is possible to use our knowledge of cancer cell biology to actively design drugs to be more specific. However, animal tests still need to be carried out at some point.

As with any pharmaceutical, new anticancer drugs are developed in a three-step process

Step 1 - Initial discovery

A wide range of compounds, both natural and synthetic, are tested in high-capacity screens to discover molecules with useful properties.

Step 2 - Molecular modification of a known compound

A molecule that shows suitable properties is chemically altered to give it the best combination of properties to make the most effective anti-cancer drug.

Step 3 - Development into a useful pharmaceutical

Because the above process is very time-consuming and expensive, the new discovery is usually patented at this time so that the discoverers can eventually recover some of these costs. The most effective route for synthesizing the molecule is then worked out. A long process of advanced testing is then begun, ending up with

tests on patients in specialized hospitals. If the results are favorable, the drug is then able to be released for use.

The process of drug development is very long and involved, with maybe only one in ten thousand of the molecules originally tested finally being clinically used.

Radiation therapy

Radiation therapy (or radiotherapy) uses high-energy rays to kill cancer cells in a targeted area. Radiation can be administered externally by an instrument that targets radiation at the tumor area. It can also be introduced internally: needles, seeds, wires, or catheters containing a radioactive substance are placed directly in or near the tumour. Radiation treatments are painless. The side effects are usually temporary, and most of them can be treated or controlled. Radiation therapy may cause a decrease in the number of white blood cells, which help to protect the body against infections. With external radiation, it is also common for the patient to suffer temporary hair loss in the treated area and for the skin to become red, dry, tender, and itchy.

External radiation does not cause body radioactivity. With internal radiation (or implant radiation), the patient may need to stay in the hospital, separated from others, while the radiation level is at its peak. Implants may be permanent or temporary. The amount of radiation in a permanent implant decreases to a safe level before the patient leaves the hospital. With a temporary implant, no radioactivity is left in the body after the implant is removed [6].

Hormone therapy

Hormone therapy is used to treat cancers that depend on hormones for their growth. It works by preventing cancer cells from getting or using the hormones they need to grow. This treatment may include the use of drugs that either stop the production of certain hormones or change the way hormones work. Another type of hormone therapy is surgery to remove organs that produce hormones. For example, the ovaries may be removed to treat breast cancer, or the testicles may be removed to treat prostate cancer.

Hormone therapy can cause a number of side effects: tiredness, fluid retention, weight gain, hot flashes, nausea and vomiting, changes in appetite, and, in some cases, blood clotting. Hormone therapy may also cause loss of bone substance in pre-menopausal women. Depending on the type of hormone therapy used, these side effects may be temporary, long lasting, or permanent.

Biological therapies

Biological therapies use the body's immune system, either directly or indirectly, to fight the disease and to alleviate some of the side effects of cancer treatment. Monoclonal antibodies, interferon, interleukin-2, and colony stimulating factors are some of the pharmaceutical molecules used here. The side effects caused by biological therapies vary according to the specific treatment. In general, these treatments tend to cause flu-like symptoms, such as chills, fever, muscle aches, weakness, loss of appetite, nausea, vomiting, and diarrhoea. Patients also may bleed or bruise easily, get a skin rash, or suffer swelling. These problems may be severe, but they usually vanish after the treatment is finished.

RNAi technology

RNAi is a naturally occurring mechanism that controls gene expression at the post-transcriptional level. With the development of genome-wide RNA interference (RNAi) approaches, the cost and time that are involved in target identification, validation and other aspects of drug discovery could be significantly reduced. In eukaryotes, double-stranded interfering RNAs target complementary mRNAs for degradation; this results in the selective silencing of specific proteins. This characteristic of RNAi makes it a valuable laboratory research tool, both in cells and in whole animal models. The development of RNAi libraries, which are composed of reagents that systematically target every gene in the genome, has made it possible to conduct high throughput screens that interrogate phenotypes associated with the loss-of-function of many genes simultaneously. By suppressing gene expression and therefore protein function, RNAi, to a certain extent, models the pharmacological inhibition of a target protein and is therefore an effective tool for proof-of-principle experiments to identify and validate cancer drug targets.

The phenomenon of RNAi was originally described in plants in the early 1990s6. RNAi is thought to have evolved to protect the host against viruses and rogue genetic elements such as transposons that utilize double-stranded RNA (dsRNA) for self-propagation [7-8]. Experimentally, long dsRNA can be used to silence target gene expression in various organisms including the nematode *Caenorhabditis elegans*, fruit flies (*Drosophila melanogaster*) and plants.

Future directions

RNAi screens have the potential to identify the key genes that control disease progression, and could also have a significant role in improving the specificity of lead compounds and the final approved drug. For target identification the benefits of RNAi screens are obvious, and screens have already been useful in the identification of critical genes that control cancer-associated phenotypes. The approach of using synthetic lethality together with RNAi also shows promise and it is hoped that this will identify targets that are more selective for tumour cells that harbour specific mutations while sparing normal cells [9].

Although the advantage of using RNAi for target identification and validation are clear, significant advancements could also be made by using RNAi in the later stages of drug discovery. The power of using RNAi in combination with expression profiling, and the recently published Connectivity Map, is persuasive and provides a complementary mechanism for the identification of compounds that specifically inhibit target proteins. It is possible that high-throughput proteomic profiling could

also be combined with RNAi and small-molecule experiments to further inform drug development. Improved clinical candidate specificity will decrease the problem of off-target toxicity associated with many compounds. Taken together, these applications suggest that RNAi will play a significant and increasing role in cancer drug discovery in the future [10].

DISCUSSION AND CONCLUSION

A very basic but important finding is this article is that cancer is not only a very severe, but also a very complex and very heterogeneous disease. In fact, it is not one single disease, but a group of many different diseases, with several common and with many differing characteristics. This is the main reason why searching for better cancer therapies is so difficult. So with the help of recent advancement in cancer discovery it will easy to treat various types of cancer. The use of RNAi screens to identify and validate novel targets is powerful, but there are significant limitations. As screens are conducted in cell lines, the significance of targets must be validated in clinical samples.

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