Targeting the thioredoxin system in the treatment of certain cancers

In the fourth and final science article on cancer treatments, Adam Todd, Roz J. Anderson, Grace Pickles and Paul W. Groundwater look at the thioredoxin system and its association with cancer, and how it offers a new therapeutic target for anticancer drug design.

So far, this series of cancer articles has reviewed traditional cancer chemotherapy approaches and their limitations (PJ, 7 November 2009, p511), examined a novel antitumour agent in clinical trials (PJ, 2/9 January 2010, p23) and looked at the potential anticancer activity of a natural product (PJ, 6 February 2010, p137). This article will examine an enzyme system — the thioredoxin system — which may have a role to play in the pathophysiology of certain cancers and offers a new therapeutic target for anticancer drug design, which could lead to the discovery of novel anticancer agents.

Thioredoxin is a small cytosolic protein, consisting of 104 amino acids, which is classed as an oxidoreductase protein because it is involved in maintaining the redox homeostasis of the cell (essentially, the balance between reduction and oxidation) (see Figure 1). There are three different thioredoxin isoforms, which are encoded by separate genes: cytosolic thioredoxin (Trx1), mitochondrial thioredoxin (Trx2), and thioredoxin highly expressed in spermatozoa (SpTrx). The most studied thioredoxin is the classic Trx1, which is the main focus of this article.

Trx1

Trx1 has two catalytic cysteine residues that can be either oxidised or reduced, depending on the redox conditions of the cell. Cysteine is an amino acid containing a thiol group (SH) and is commonly found in proteins. These cysteine residues allow thioredoxin to act as an antioxidant, which therefore helps protect against oxidative stress. Thioredoxin reductase (the second part of the thioredoxin system) is responsible for converting oxidised thioredoxin back to the reduced form, thus regenerating thioredoxin’s antioxidant ability. Thioredoxin and thioredoxin reductase make up what is collectively known as the “thioredoxin system.”

Over the years, research has shown that cancer is a complicated, polygenic and dynamic disease that can occur when there is an imbalance between the formation of oncogenes (genes that, when activated, can cause cancer) and tumour suppressor genes (genes that help prevent cancer). This imbalance can arise as a consequence of DNA base mutations (caused by smoking cigarettes, for example) and can disrupt the normal balance of cell proliferation and differentiation, often leading to cancer. Hanahan and Weinberg have previously suggested that changes in six fundamental cell physiological processes can result in the initiation of cancer (see Panel).

In addition to maintaining the redox homeostasis, it would appear that the thioredoxin system may also have a role in the development of cancer by supporting several of the cancer cell modifications described by Hanahan and Weinberg.

Since its discovery, the thioredoxin system has been the subject of many studies that have revealed that thioredoxin over-expression is related to poor prognosis in lung cancer, gastric cancer and colorectal cancer.

DNA synthesis

Thioredoxin also has a role in the synthesis of DNA by providing reducing equivalents for ribonucleotide reductase, an enzyme responsible for generating deoxyribonucleotides, which are key intermediates in DNA synthesis. Inhibition of thioredoxin (either directly, by inhibiting thioredoxin, or indirectly, by inhibiting thioredoxin reductase) could therefore disrupt the normal synthesis of DNA. Because tumours need a plentiful supply of deoxyribonucleotides to synthesise DNA, disrupting cancer cell modifications

There are six fundamental cell physiological processes that can lead to tumour formation:

1. Self-sufficiency in growth signals
2. Insensitivity to growth inhibitory signals
3. Evasion of apoptosis (programmed cell death)
4. Limitless replicative potential
5. Sustained angiogenesis
6. Tissue invasion and metastasis
Angiogenesis

Angiogenesis, another important feature of cancer, is the growth of new blood vessels from pre-existing vessels and is often required for the development of solid tumours. It is a well synchronised and compartmented process, with several studies highlighting the implication of the thioredoxin system in hypoxic conditions (low levels of oxygen), a tumour will secrete proteins to stimulate angiogenesis in order to replenish oxygen and nutrient levels.

One example of an angiogenic protein is hypoxia-inducible factor-1 (HIF-1). It is capable of upregulating several genes, including the gene for vascular endothelial growth factor (VEGF), which promotes angiogenesis. It has been shown that reduced thioredoxin can increase HIF-1α levels, causing increased VEGF production and, ultimately, increased tumour angiogenesis. The inhibition of thioredoxin signalling could therefore lead to a reduction in the levels of VEGF and a disruption of subsequent angiogenesis.

Thioredoxin is accepted as a realistic and rational drug target and there are a number of thioredoxin inhibitors in development, two of which, Px-12 and PMX-464, are discussed below.

Px-12

Px-12 (1-methylpropyl 2-imidazolyl disulphide) is an irreversible inhibitor of thioredoxin and was the first thioredoxin inhibitor to enter clinical trials (see Figure 2). It is thought that Px-12 irreversibly inhibits thioredoxin by forming a covalent bond with a non-catalytic cysteine residue of thioredoxin. The progress of Px-12 was reported at the recent American Society of Clinical Oncology conference.12 Px-12 is well tolerated up to doses of 400 mg/m²/day and stable disease was achieved in three patients with advanced solid tumours. Minor side effects were reported with Px-12 and include fatigue, taste disturbance and, notably, halitosis, caused by the expiration of a Px-12 metabolite.

PMX-464

Another thioredoxin inhibitor in development is PMX-464 (formerly called AW464), which is thought to inhibit thioredoxin irreversibly through the formation of covalent bonds with the two catalytic cysteine residues of thioredoxin. PMX-464 has shown good activity in colon, renal and certain breast cancer cell lines. Pharminox, the company that is developing PMX-464, has also developed PMX-2058, a water-soluble prodrug of PMX-464, which is a lead candidate in its drug discovery pipeline. PMX-2058 is yet to undergo clinical trials but has scheduled to enter regulatory toxicity studies in late 2009.

Traditional chemotherapy

Interestingly, retrospective studies on a number of conventional anticancer agents used in cancer drug screening have revealed that some are also potent inhibitors of the thioredoxin system and these include cisplatin, doxorubicin, cyclophosphamide, melphalan, and chlorambucil, although further research is needed to ascertain whether this activity contributes to the observed cytotoxicity of these agents.

Conclusion

Advances in the treatment of certain cancers have been made recently through a move away from traditional to more targeted chemotherapy. Targeted therapies offer a unique and attractive anticancer treatment because they are rational drug targets and offer a unique and attractive anticancer treatment. For this progress to continue, it is paramount that research into the molecular mechanisms of cancer continues.

One biological system that would appear to have a role in the thioredoxin system is the thioredoxin system supports carcinogenesis through a number of mechanisms, some of which are outlined by Hanahan and Weinberg.7 Inhibition of this system could target several of these mechanisms, namely DNA replication, apoptosis and angiogenesis. Thioredoxin inhibitors have the potential to show a promising range of anticancer activity and thus offer a unique and attractive anticancer therapeutic target.

References