Photodynamic Therapy (PDT)

The main use of photochemistry in medicine is in photodynamic therapy (PDT), which is widely used to treat cancers. In photodynamic therapy, a photosensitiser - a light - activated drug - is injected, drunk, or otherwise introduced into the body, and left to accumulate in tumour tissue. This tissue is then illuminated with a specific wavelength of light, which leads to necrosis and apoptosis.

Clinical Procedure

In photodynamic therapy two ingredients that are non-toxic on their own - a photosensitiser and light - combine, in the presence of oxygen to kill cells. The procedure is shown in Fig. 1:

1. Photosensitiser injected, drunk, or topically applied to the skin.

2. Photosensitiser accumulates in tumours and mostly clears from healthy tissue.

3. Laser irradiation incident on the photosensitisers makes them generate toxic species.

4. The toxicity causes cell necrosis and apoptosis predominantly in the tumours.

5. The immune system clears up the dead cells and attacks remaining malignant cells.

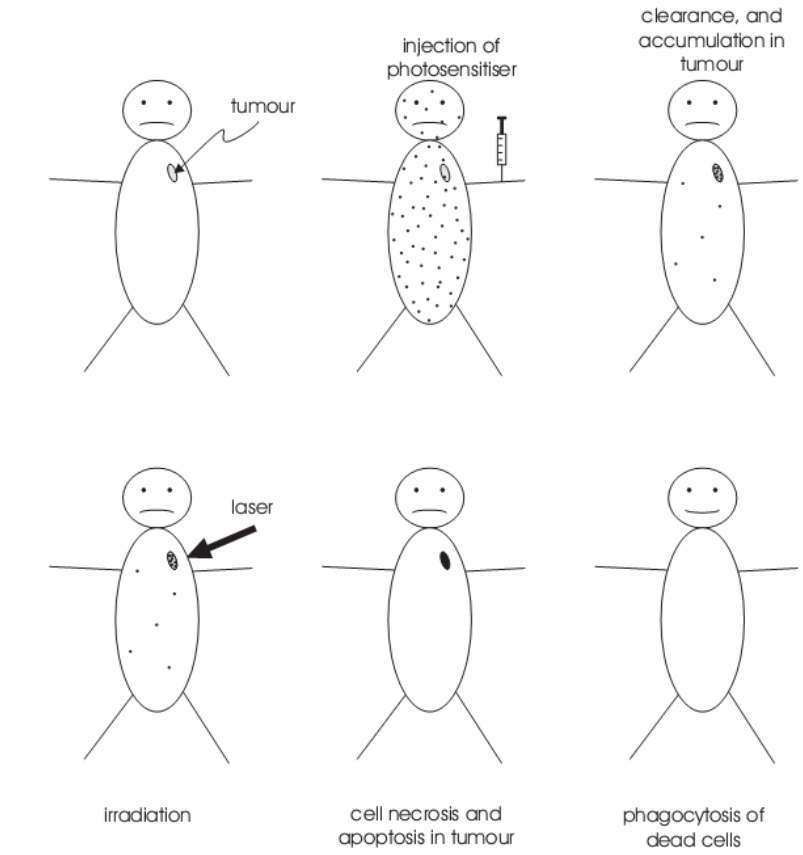

Figure 1: Photodynamic therapy procedure for cancer treatment.

Applications

There are many potential applications for PDT, but few currently used clinically. Some of the conditions for which PDT is more likely to be a standard treatment are listed below.

- Very early lung cancers - a bronchoscope is used to deliver the light.
- skin - basal cell carcinoma, squamous cell carcinoma, pre-cancerous actinic keratosis (but not melanoma which metastatises too quickly and is often too pigmented to allow light to penetrate).
- Oesophagus - pre-malignant (dysplastic) Barrett's oesophagus. (Currently the standard treatment is with RF ablation - electrically-induced thermal necrosis).
- Head and neck tumours - good cosmetic results, reduced scarring compared to conventional surgery.
- Arterial disease - prevents restenosis (re-narrowing of an artery) after angioplasty.
- `Mopping up' following radiotherapy.
- Ophthalmology - age-related macular degeneration (AMD)

Mechanisms and Pathways

PDT works by generating highly toxic reactive oxygen species (ROS) to kill cells. The term `reactive oxygen species' encompasses a number of different molecules, including peroxides, free radicals, oxygen ions, etc. all of which are highly reacting, and therefore react with, and damage, cellular components and the cell membrane. This causes both necrosis and apoptosis (the two known types of cell death).

When a photosensitive molecule is in its singlet ground state, call it ^1P , and it absorbs a photon, it is put into an excited singlet state, $^1P^*$. Then, one of several things can happen:

1. Non-radiative singlet decay, $^1P^* \longrightarrow {}^1P$, with the energy being lost through vibrational relaxation. (Not what we are interested in here.)

2. Radiative singlet decay, $^1P^* \longrightarrow {}^1P + h\nu$, i.e. fluorescence, lower energy photon emitted a few nanoseconds after absorption. Photosensitisers often exhibit fluorescence and so can be used to detect as well as treat tumours.

3. Conversion to a triplet state via an intersystem crossing.

If one of the energy levels for P in an excited singlet state, $^1P^*$, happens to be similar to an energy level with P in an excited triplet state, $^3P^*$, then the molecule may convert to this triplet state: this is called an intersystem crossing. The triplet state is a relatively stable and long-lived state, and can undergo reactions that result in ROS.

There are thought to be two main types of reaction, imaginatively named Type I and Type II. These are shown in Fig. 2. The Type II reaction, which creates excited singlet oxygen $^1O^*_2$, a very reactive species, from the usual triplet form $^3O_2$ is considered the most important for photodynamic therapy.

The generation of cytotoxic ROS in PDT requires the presence of oxygen, eg. if the tissue is clamped to prevent blood from reoxygenating the tissue so the tissue becomes hypoxic (lack of oxygen) then photodynamic therapy does not work.

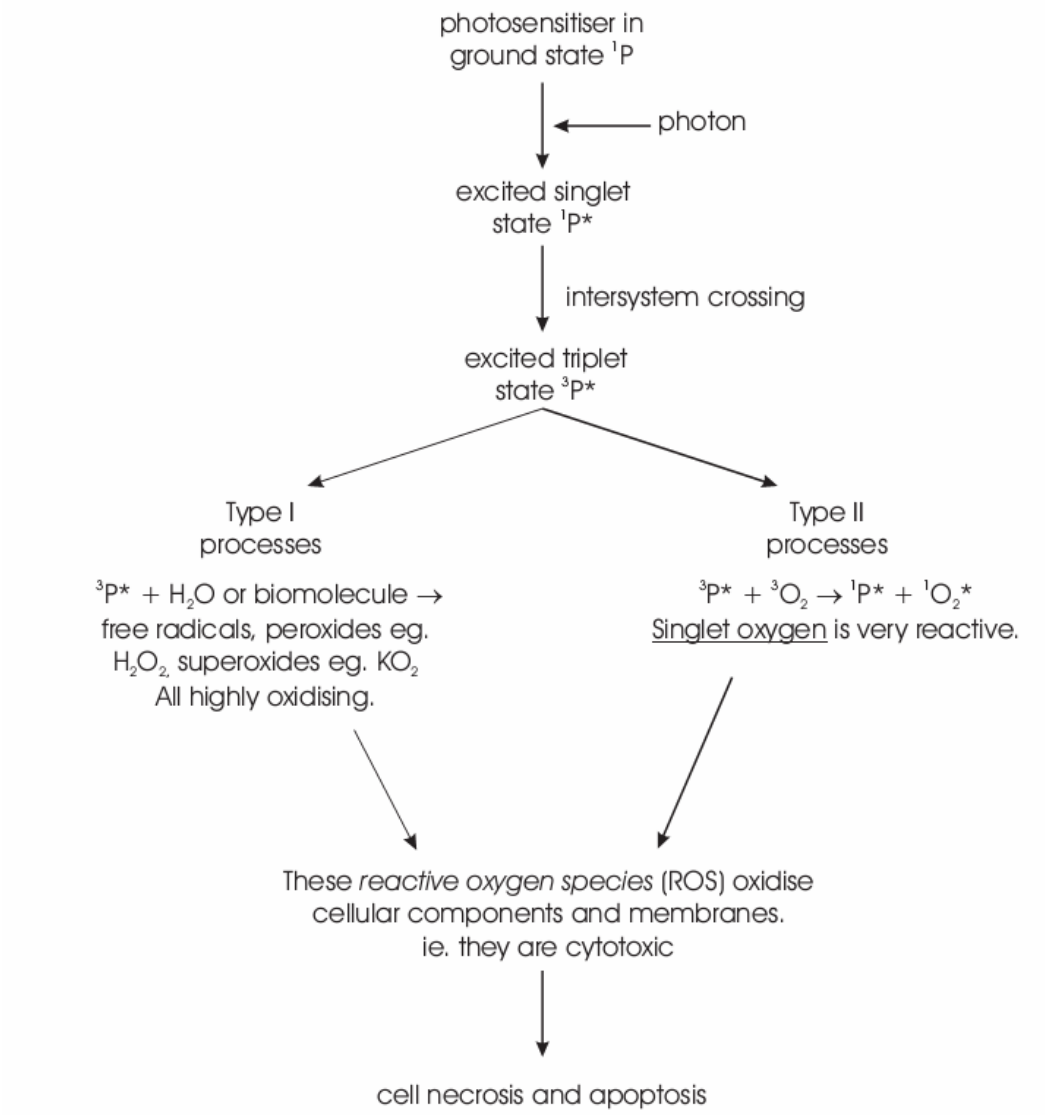

Figure 2: Mechanisms of photodynamic therapy.

Photosensitisers

There are several classes of photosensitiser, with porphyrin-related photosensitisers being the most important and the most widely used. The details of three key photosensitisers are given below. New candidate photosensitisers are becoming available (eg. Visudyne, WST11, Lu-Tex) and research continues on novel and improved photosensitisers for particular applications, often treating tumors.

Ideal photosensitiser is:

- Chemically pure and of known composition,
- Only cytotoxic in the presence of light,
- Highly efficient, ie. high quantum yield (many ROS generated per photon),
- Activated in the range 630-800 nm where tissue is most transparent (so can reach deep tissue) and photons are still energetic enough to generate ROS,
- Rapidly cleared from the body (so quality of life is not unduly affected and repeat treatments are possible),
- Preferentially retained by the target tissue, eg. tumour (not always important in practice, but clearly a useful property).

Hematoporphyrin derivative (pormer sodium, HpD, λ_{Act} = 630 nm) was the first photosensitiser used in PDT. HpD contains several different porphyrins. Photofrin was the first commercially available photosensitiser for PDT. It can take several weeks to completely clear from the body, and patients are advised to avoid direct sunlight or bright indoor lighting for 30+ days after injection. Photofrin is used to treat endobronchial cancer.

5-aminolaevulinic acid (ALA, λ act= 635 nm) generates a photosensitiser endogenously called protoporphyrin IX (PpIX). PpIX tends to accumulate in mucosal tissue because, being metabolically more active, they convert more PpIX from ALA. Other advantages of ALA are that it clears in 24-36 hours, thus reducing the duration for which the skin is light sensitive. It has been used to treat basal cell carcinoma, head and neck tumours, gynaecological tumours, acne and other types of cosmetic surgery.

Meta-tetrahydroxyphenyl chlorin (m-THPC, Foscan R, λact= 652 nm) is considerably more effective than Photofrin allowing much lower doses to be used. It is also activated at a longer wavelength allowing deeper tumours to be treated. It has been used to treat head and neck tumours, but because of its much higher efficiency much greater care must be taken to avoid sunlight and other unwanted sources of light. Another disadvantage is that its clearance rate is much slower than ALA, with patients advised to avoid bright lights for several weeks and sunbathing for perhaps 3 months.

PDT-Induced Anti-Tumour Immunity

An acute inflammatory response follows the necrosis or apoptosis of the cells due to the cytotoxic ROS produced during PDT. There is some evidence that this mediates an anti-tumour immune response. Roughly, following cell death, antigens (bits of the cell and its contents) are phagocytosed by dendritic cells, which travel to lymph nodes and present the antigens to T lymphocytes, which are activated into effector T cells, which migrate to the tumour and kill the cancerous cells. This is an exciting prospect because, if this effect is found to be significant, the tumour may continue to be destroyed by the immune system even after PDT treatment, and may even leave some longer term protection against similar tumours

recurring. It has also been suggested that this sort of approach may be used to develop novel cancer vaccines, by using PDT on cell cultures.