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Emerging therapy for Cancer

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Abstract

Cancer therapy is evolving with advances in immunotherapy, targeted therapies, and precision medicine, offering more personalized and effective treatment options. Immunotherapies like check point inhibitors and CAR-T cell therapy show promise in boosting the body immune response against cancer cell. Precision medicine tailors treatment based on a person's genetic makeup, enhancing the chances of success. Research in these areas continues to shape the future of cancer area. Conventional treatments approaches, such as surgery, chemotherapy, and radiotherapy, have been in use while significant advances are being made in recent time including stem cell therapy, targeted therapy, ablation therapy, nanoparticles, natural oxidants, radionics, chemodynamic therapy, sonodynamic therapy, and ferroptosis based therapy. Stem cells therapy has brought promising efficacy in regenerating and repairing diseased or damaged tissues by targeting both primary and metastatic cancer foci, and nanoparticles brought new diagnostic and therapeutic options. Targeted therapy possessed break through potential inhibiting the growth and spread of specific cancer cell, causing less damage to healthy cells. Ablation therapy has emerged as a minimally invasive procedure that burns or freezes cancers without the need for open surgery. Natural antioxidants demonstrated potential tracking down free radicals and neutralizing their harmful effects thereby treating and preventing cancer. Several technologies are currently under research in clinical trails, and some of them have already been approved. This review presented an update on recent advances and break through in cancer therapies.

Keywords: chemotherapy, stem cell therapy, nanoparticles, natural oxidants, ablation therapy

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Contents

1. Introduction.....	10
2. Pathophysiology.....	12
3. Targeted therapies.....	13
4. Conclusion.....	15
5. References.....	16

1. Introduction

Cancer is a global health problem responsible for one in six deaths worldwide. In 2020, there were an estimated 19.3 million new cancer cases and about 10 million cancer deaths globally. Cancer is a very complicated sequence of disease conditions progressing gradually with a generalized loss of growth control. There were only a few options of cancer treatment for patients for many decades which include surgery, radiation therapy, and chemotherapy as

single treatments or in combination. But recently, many pathways involved in cancer therapy progression and how they can be targeted has improved dramatically, with combinatorial strategies, involving multiple targeted therapies or “traditional” chemotherapeutics, such as the taxanes and platinum compounds, being found to have a synergistic effect. 2New approaches, such as drugs, biological molecules, and immune-mediated therapies, are

being used for treatment even if the expected therapy level has not reached that resists the mortality rate and decreases the prolonged survival time for metastatic cancer. The creation of a new revolution in neoplastic cancer or targeting drugs depends on the pathways and characteristics of different tumor entities. Chemotherapy is considered the most effective and widely used modality in treating cancers as used alone or in combination with radiotherapy.³ Genotoxicity is how chemotherapy drugs target the tumor cells mainly producing reactive oxygen species that largely destroy tumor cells. Hormonal treatments are also widely used for cancer malignancies and considered as cytostatic because it restricts tumor development by limiting the hormonal growth factors acting through the direction of hypothalamic–pituitary–gonadal axis (HPGA), hormone receptor blockage, and limiting of adrenal steroid synthesis. In this narrative review, a general overview of the most advanced and novel cancer therapies was provided. In addition, also new strategies currently under investigation at the research stage that should overwhelm the drawbacks of standard therapies; different strategies to cancer diagnosis and therapy; and their current status in the clinical context, underlining their impact as innovative anti-cancer approaches.

Colorectal cancer (CRC) is the third most common malignancy worldwide and is projected to increase by 3.2 million new incident cases and account for 1.6 million deaths by 2040. Up to 25% of individuals with CRC present with stage IV disease and approximately 25%-50% who initially present with early-stage CRC go on to develop metastases. ⁵Stage IV CRC has a 5-year survival of 12.5% in the United States, and thus, the development of safe, effective, and tolerable therapy represents an urgent clinical need. Metabolic reprogramming is one of the crucial hallmarks of cancer. To sustain continuous proliferation and metastasis, tumor cells undergo several metabolic adaptations to cope with the nutrient-deficient microenvironment. Research on cancer metabolism began a century ago with the pioneering work of Otto Warburg, who observed that tumor cells in vitro exhibited a preference for utilizing aerobic glycolysis and producing lactate. ⁶This phenomenon came to be known as the “Warburg effect.” Since then, a variety of metabolic reprogramming events have been revealed in tumor cells, including an expanded need for electron acceptors, elevated reliance on oxidative stress protection, and increased demand for nitrogen. Recent technological advances further demonstrate that cancer metabolism is temporally and spatially heterogeneous.

History and etiology of cancer: Origin of Cancer

- The disease was first called cancer by Greek physician Hippocrates [460-370]. He is considered the “Father of medicine.” Hippocrates used terms carcinos and carcinoma to describe non ulcer forming and ulcer-forming tumors.
- Later Roman physician, Celsus [28-50BC] translated the Greek term cancer, the Latin word for carb. It was Galen [130-200AD], another Roman

physician, who was the term oncos to describe tumors. Oncos is the root word for oncology or study of cancer ¹.

Between 15th and 18th Centuries

During the beginning of the 15th century scientists developed greater understanding of the workings human body and its diseases. Autopsies, done by Harvey [1628], led to an understanding of the circulation of blood through the heart and blood. Giovanni Moragagni of Pundain 1761 regularized autopsies to find the cause of diseases. The laid foundation for the study of cancer as well. It was Scottish surgeon John Hunter [1728-1793] who suggested that some cancers might be cured by surgery. It was nearly a century later that development of anesthesia prompted regular surgery for “Movable” cancer that had not spread to other organs.

The 19th Century Rudolf Virchow, often called the founder of cellular pathology, founded the basis for pathologic study of cancers under the microscope. Virchow correlated microscopic pathology to illness. He developed study of tissues that were taken out after surgery. The pathologist could also tell the surgeon whether the operation had completely removed the cancer.

History of the Causes of Cancer

There have been numerous theories of causes of cancer throughout ages. For example, the ancient Egyptians blamed god for cancers. Hippocrates believed that the body had 4 humors: blood, phlegm, yellow bile, black bile. He suggested that an imbalance of these humors with an excess of black bile in various body sites could cause cancer. This was the humoral theory. After humoral theory came the lymph theory. Stahl and Hoffman theorized that cancer was composed of fermenting and degenerating lymph, varying in density, acidity, and alkalinity. John Hunter, the Scottish surgeon from the 1700s, agreed that tumors grow from lymph constantly released from blood. ⁷Zacutus Lusitani [1575-1642] and Nicholas Tulp [1593-1642], doctors in Holland, concluded that cancer was contagious. It was in 1838 that German pathologist Johannes Muller showed that cancer is made up of cells rather than lymph. Muller proposed that cancer cells developed from budding elements between normal tissues. Rudolph Virchow [1821-1902], suggested that all cells, including cancer cells, are derived from other cells. He proposed the chronic theory. He believed that cancer spread like a liquid. In the 1860s, German surgeon, Karl Thiersch, showed that cancer metastasize through the spread of malignant cells and not through a liquid. Until the 1920s, trauma was thought to be the cause of cancer.

Etiological agents environmental factors;

Tobacco, smokers, diets, environmental pollutants, etc. Heavy smoking causes lung, oral cavity and oesophagus cancer. Excessive intake of alcohol causes liver cancer. **CHEMICAL CARCINOGEN** Nickel compounds, cadmium, arsenic, nitrosamines, trichloroethylene, arylamines, benzopyrene, aflatoxins, reactive oxygen radicals, etc. **Physical Carcinogen** UV rays, ionizing radiation [x-rays and gamma rays]

Biological Carcinogen Virus:

has also been associated with various types of cancer. These viruses are called oncoviruses. Rous sarcoma virus is the first discovered retro-virus causing cancer; Human papilloma virus, Epstein -barr virus, Hepatitis B virus, Herpes virus

BACTERIA: Helicobacter pylori.

Endogenous Factors

Mutations, change in DNA replication, metabolic reactions generating, reactive oxygen radicals, immune system factors, Ageing.¹⁰

2. Pathophysiology

Pathophysiology is a combination of two medical terms; pathology and physiology, pathology involves the study of structural and functional changes in cells, tissue, or organs that are caused by a particular disease. On the other hand, physiology explores the functions of the human body. Therefore, pathophysiology can be defined as the study of fundamental changes in the body's physiology, resulting from a disease.¹³ For instance, the pathophysiology of the tumor explores the underlying changes in the body that results from the tumor or metastasis of cancer cells. Therefore, the pathophysiology of cancer includes the physical and hormonal changes associated with cancer and paraneoplastic syndrome.¹³ In general, cancer occurs in four main stages. The pathological stage of cancer is determined through biopsy (removal of small body tissue for laboratory examination) where the cancerous cells are compared to normal cells. The four main stages of cancer are:

Stage 1 — Cancer is normally localized in a small area

Stage 2 — The size of the cancer increases

Stage 3 — The size of cancer becomes larger and starts spreading to some parts of the body including lymph nodes

Stage 4 — Cancer has grown and has spread to most parts of the body.¹³

Diagnosis

Cancer screening Diagnosing cancer at its earliest stages often provides the best chance for a cure. With this in mind, talk with your doctor about what types of cancer screening may be appropriate for you. For a few cancers, studies show that screening tests can save lives by diagnosing cancer early. For other cancers, screening tests are recommended only for people with increased risk.¹⁴ A variety of medical organizations and patient-advocacy groups have recommendations and guidelines for cancer screening. Review the various guidelines with your doctor and together you can determine what's best for you based on your own risk factors for cancer diagnosis. Your doctor may use one or more approaches to diagnose cancer: Physical exam. Your doctor may feel areas of your body for lumps that may indicate cancer. During a physical exam, your doctor may look for abnormalities, such as changes in skin colour or enlargement of an organ, that may indicate the presence of cancer.¹⁴ Laboratory tests, Laboratory tests, such as urine and blood tests, may help your doctor identify abnormalities that can be caused by cancer. For instance, in people with leukemia, a common blood test called complete blood count may reveal an unusual number or type of white blood cells.

Imaging tests:

Imaging tests allow your doctor to examine your bones and internal organs in a non-invasive way. Imaging tests used in diagnosing cancer may include a computerized tomography (CT) scan, bone scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, ultrasound and X-ray, among others.¹⁴ Biopsy. During a biopsy, your doctor collects a sample of cells for testing in the laboratory. There are several ways of collecting a sample. Which biopsy procedure is right for you depends on your type of cancer and its location. In most situations, a biopsy is the only way to definitively diagnose cancer.¹⁴

Cancer therapy Development

Cancer treatments are a wide range of treatments available for the many different types of cancer, with each cancer type needing its own specific treatment. Treatments can include surgery, chemotherapy, radiation therapy, hormonal therapy, targeted therapy including small-molecule drugs or monoclonal antibodies,^[2] and PARP inhibitors such include hyperthermia, immunotherapy, photodynamic therapy, and stem-cell therapy as olaparib. Other therapies:^[4] Most commonly cancer treatment involves a series of separate therapies such as chemotherapy before surgery.^[4]

Angiogenesis inhibitors are sometimes used to enhance the effects of immunotherapies.^[5] The choice of therapy depends upon the location and grade of the tumor and the stage of the disease, as well as the general state of the patient. Biomarker testing can help to determine the type of cancer, and indicate the best therapy.^[6] A number of experimental cancer treatments are continuously under development. In 2023 it was estimated that one in five people will be diagnosed with cancer at some point in their lifetime.^[1]

The primary goal of cancer treatment is to either cure the cancer by its complete removal, or to considerably prolong the life of the individual. Palliative care is involved when the prognosis is poor and the cancer termed as terminal. There are many types of cancer, and many of these can be successfully treated if detected early enough.^[1] Types of treatments The treatment of cancer has undergone evolutionary changes as understanding of the underlying biological processes has increased.

Tumor removal surgeries have been documented in ancient Egypt, hormone therapy and radiation therapy were developed in the late 19th century. Chemotherapy, immunotherapy and newer targeted therapies are products of the 20th century. As new information about the biology of cancer emerges, treatments will be developed and modified to increase effectiveness, precision, survivability, and quality of life. Surgery[edit] Malignant tumours can be cured if entirely removed by surgery. But if the cancer has already spread (metastasized) to other sites, complete surgical excision is usually impossible. In the Halstedian model of cancer progression, tumors grow locally, then spread to the lymph nodes, then to the rest of the body.

This has given rise to the popularity of local-only treatments such as surgery for small cancers. Even small localized tumors are increasingly recognized as possessing metastatic potential. Examples of surgical procedures for cancer include mastectomy, and lumpectomy for breast cancer, prostatectomy for prostate cancer, and lung cancer surgery for nonsmall cell lung cancer. The goal of the surgery can be either the removal of only the tumor, the entire organ, or part of the organ.^[7]

A single cancer cell is invisible to the naked eye but can regrow into a new tumor, a process called recurrence. For this reason, the pathologist will examine the surgical specimen to determine if a margin of healthy tissue is present, thus decreasing the chance that microscopic cancer cells are left in the patient. In addition to removal of the primary tumor, surgery is often necessary for staging, e.g. determining the extent of the disease and whether it has metastasized to regional lymph nodes. Staging is a major determinant of prognosis and of the need for adjuvant therapy. Occasionally, surgery is necessary to control symptoms, such as spinal cord compression or bowel obstruction. This is referred to as palliative treatment. Surgery may be performed before or after other forms of treatment. Treatment before surgery is often described as neoadjuvant. In breast cancer, the survival rate of patients who receive neoadjuvant chemotherapy are no different from those who are treated following surgery.^[8] Giving chemotherapy earlier allows oncologists to evaluate the effectiveness of the therapy, and may make removal of the tumor easier.

However, the survival advantages of neoadjuvant treatment in lung cancer are less clear. Radiation therapy Radiation therapy (radiotherapy) is the use of ionizing radiation to kill cancer cells and shrink tumors by damaging their DNA causing cellular death.^[9] Radiation therapy can either damage DNA directly or create charged particles (free radicals) within the cells that can in turn damage the DNA. Radiation therapy can be administered externally via external beam radiotherapy or internally via brachytherapy.

The effects of radiation therapy are localised and confined to the region being treated. Although radiation damages both cancer cells and normal cells, most normal cells can recover from the effects of radiation and function properly. The goal of radiation therapy is to damage as many cancer cells as possible, while limiting harm to nearby healthy tissue. Hence, it is given in many fractions, allowing healthy tissue to recover between fractions. Radiation therapy may be used to treat almost every type of solid tumor, and may also be used to treat leukemia and lymphoma⁸. Radiation dose to each site depends on a number of factors, including the radio sensitivity of each cancer type and whether there are tissues and organs nearby that may be damaged by radiation. Thus, as with every form of treatment, radiation therapy is not without its side effects. Radiation therapy can lead to dry mouth from exposure of salivary glands to radiation, resulting in decreased saliva secretion. Post therapy, the

salivary glands will resume functioning but rarely in the same fashion.

Dry mouth caused by radiation can be a permanent problem.^[10] Radiation might not be a choice of treatment if the tumor was diagnosed in late stages or is in a vulnerable location, as radiation might be more likely to cause damage to organs at effective doses. Moreover, radiation therapy for patients under 14 can cause particularly significant long-term side effects, such as hearing loss and blindness, that influence the lifestyle of the young patients. Children who had received cranial radiotherapy are deemed at a high risk for academic failure and cognitive delay.¹¹ Chemotherapy Chemotherapy is the treatment of cancer with drugs ("anticancer drugs") that can destroy cancer cells. Chemotherapy can be given in a variety of ways such as injections into the muscles, skin, artery, or vein, or it could even be taken by mouth in the form of a pill.^[11] In current usage, the term "chemotherapy" usually refers to cytotoxic drugs which affect rapidly dividing cells in general, in contrast with targeted therapy (see below). Chemotherapy drugs interfere with cell division in various possible ways, e.g. with the duplication of DNA or the separation of newly formed chromosomes.

Most forms of chemotherapy target all rapidly dividing cells and are not specific to cancer cells, although some degree of specificity may come from the inability of many cancer cells to repair DNA damage, while normal cells generally can. Hence, chemotherapy has the potential to harm healthy tissue, especially those tissues that have a high replacement rate (e.g. intestinal lining). These cells usually repair themselves after chemotherapy. Because some drugs work better together than alone, two or more drugs are often given at the same time. This is called "combination chemotherapy"; most chemotherapy regimens are given in a combination.^[12]

3. Targeted therapies

Targeted therapy, which first became available in the late 1990s, has had a significant impact in the treatment of some types of cancer, and is currently a very active research area. This constitutes the use of agents specific for the deregulated proteins of cancer cells. Small molecule drugs are targeted therapy drugs that are generally inhibitors of enzymatic domains on mutated, overexpressed, or otherwise critical proteins within the cancer cell. Prominent examples are the tyrosinekinase inhibitors imatinib (Gleevec/Glivec) and gefitinib (Iressa).¹³

Monoclonal antibody therapy is another strategy in which the therapeutic agent is an antibody which specifically binds to a protein on the surface of the cancer cells. Examples include the anti-HER2/neu antibody trastuzumab (Herceptin) used in breast cancer, and the anti-CD20 antibody rituximab, used in a variety of B-cell malignancies.¹⁴ Targeted therapy can also involve small peptides as "homing devices" which can bind to cell surface receptors or affected extracellular matrix surrounding the tumor. Radionuclides which are attached to these peptides

(e.g. RGDs) eventually kill the cancer cell if the nuclide decays in the vicinity of the cell.¹⁵ Especially oligo- or multimers of these binding motifs are of great interest, since this can lead to enhanced tumor specificity and avidity.

Photodynamic therapy (PDT) is a ternary treatment for cancer involving a photosensitizer, tissue oxygen, and light (often using lasers). PDT can be used as treatment for basal cell carcinoma (BCC) or lung cancer; PDT can also be useful in removing traces of malignant tissue after surgical removal of large tumors.^[14] In February 2019, medical scientists announced that iridium attached to albumin, creating a photosensitized molecule, can penetrate cancer cells and, after being irradiated with light, destroy the cancer cells. High-energy therapeutic ultrasound could increase higher-density anti-cancer drug load and nanomedicines to target tumor sites by 20x fold higher than traditional target cancer therapy.

Targeted therapies under pre-clinical development as potential cancer treatments include morpholino splice switching oligonucleotides, which induce ERG exon skipping in prostate cancer models, multitargeted kinase inhibitors that inhibit the PI3K with other pathways including MEK and PIM, and inhibitors of NF- κ B in models of chemotherapy resistance.¹⁶

Immunotherapy

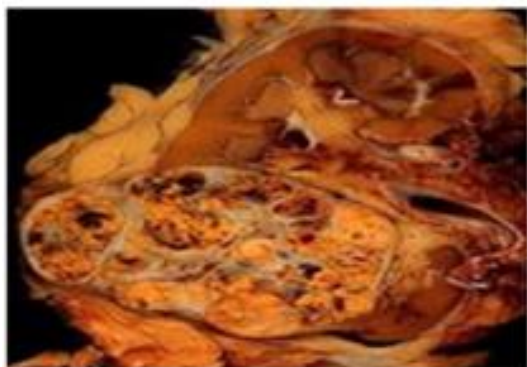


Fig.1 Cancer Liver Cell

Cancer immunotherapy refers to a diverse set of therapeutic strategies designed to induce the patient's own immune system to fight the tumor. Contemporary methods for generating an immune response against tumors include intravesical BCG immunotherapy for superficial bladder cancer, and use of interferons and other cytokines to induce an immune response in renal cell carcinoma and melanoma patients. Cancer vaccines to generate specific immune responses are the subject of intensive research for a number of tumors, notably malignant melanoma and renal cell carcinoma.¹⁷

Sipuleucel-T is a vaccine-like strategy for prostate cancer in which dendritic cells from the patient are loaded with prostatic acid phosphatase peptides to induce a specific immune response against prostate-derived cells. It gained FDA approval in 2010. Allogeneic hematopoietic stem cell transplantation (usually from the bone marrow) from a

genetically non-identical donor can be considered a form of immunotherapy, since the donor's immune cells will often attack the tumor in a phenomenon known as graft-versus tumor effect. For this reason, allogeneic HSCT leads to a higher cure rate than autologous transplantation for several cancer types, although the side effects are also more severe.¹⁸

The cell based immunotherapy in which the patients own natural killer cells (NKs) and cytotoxic T cells are used has been in practice in Japan since 1990. NK cells and TCs primarily kill the cancer cells when they are developed. This treatment is given together with the other modes of treatment such as surgery, radiotherapy or chemotherapy and termed autologous immune enhancement therapy (AIET).¹⁹

Immune checkpoint therapy focuses on two immune checkpoint proteins, cytotoxic T lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD1).²⁰ Under normal conditions, the immune system utilizes checkpoint proteins as negative feedback mechanisms to return to homeostasis once pathogens have been cleared from the body. In a tumor microenvironment, cancer cells can commandeer this physiological regulatory system to "put a brake" on the anti-cancer immune response and evade immune surveillance. 2018 Nobel Prize in medicine is awarded to Dr. James Allison of University of Texas MD Anderson Cancer Center in U.S. and Dr. Tasuku Honjo Kyoto University in Japan for their contributions in advance of PD-1 and CTLA-4 immune checkpoint therapy.

Emerging therapy of Cancer

Photodynamic therapy (PDT) is a form of phototherapy involving light and a photosensitizing chemical substance used in conjunction with molecular oxygen to elicit cell death (phototoxicity).^[1] PDT is used in treating acne, wet age-related macular degeneration, psoriasis, and herpes. It is used to treat malignant cancers,^[2] including head and neck, lung, bladder and particular skin. The technology has been tested for treatment of prostate cancer.^[3] Advantages lessen the need for delicate surgery and lengthy recuperation and minimal formation of scar tissue and disfigurement. A side effect is the associated photosensitisation of skin tissue.^[4] PDT applications involve three components:^[2] a photosensitizer, a light source and tissue oxygen. The wavelength of the light source needs to be appropriate for exciting the photosensitizer to produce radicals and/or reactive oxygen species. These are free radicals (Type I) generated through electron abstraction or transfer from a substrate molecule and highly reactive state of oxygen known as singlet oxygen (Type II).

PDT is a multi-stage process. First a photosensitiser, ideally with negligible toxicity other than its phototoxicity, is administered in the absence of light, either systemically or topically. When a sufficient amount of photosensitiser appears in diseased tissue, the photosensitiser is activated by exposure to light for a specified period.

The light dose supplies sufficient energy to stimulate the photosensitizer, but not enough to damage neighbouring healthy tissue. The reactive oxygen kills the target cells.^[4] Reactive oxygen species [edit] In air and tissue, molecular oxygen (O₂) occurs in a triplet state, whereas almost all other molecules are in a singlet state. Reactions between triplet and singlet molecules are forbidden by quantum mechanics, making oxygen relatively non-reactive at physiological conditions. A photosensitizer is a chemical compound that can be promoted to an excited state upon absorption of light and undergo intersystem crossing (ISC) with oxygen to produce singlet oxygen. This species is highly cytotoxic, rapidly attacking any organic compounds it encounters. It is rapidly eliminated from cells, in an average of 3 μs.^[5]

Photochemical processes

When a photosensitizer is in its excited state (3Psen*) it can interact with molecular triplet oxygen (3O₂) and produce radicals and reactive oxygen species (ROS), crucial to the Type II mechanism. These species include singlet oxygen (1O₂), hydroxyl radicals (•OH) and superoxide (O₂⁻) ions. They can interact with cellular components including unsaturated lipids, amino acid residues and nucleic acids. If sufficient oxidative damage ensues, this will result in target-cell death (only within the illuminated area).^[4] Photochemical mechanisms [edit] When a chromophore molecule, such as a cyclic tetrapyrrolic molecule, absorbs a photon, one of its electrons is promoted into a higher-energy orbital, elevating the chromophore from the ground state (S₀) into a short-lived, electronically excited state (S_n) composed of vibrational sub-levels (S_n').

The excited chromophore can lose energy by rapidly decaying through these sub-levels via internal conversion (IC) to populate the first excited singlet state (S₁), before quickly relaxing back to the ground state.^[4] The decay from the excited singlet state (S₁) to the ground state (S₀) is via fluorescence (S₁ → S₀). Singlet state lifetimes of excited fluorophores are very short (τ_{fl.} = 10⁻⁹–10⁻⁶ seconds) since transitions between the same spin states (S → S or T → T) conserve the spin multiplicity of the electron and, according to the Spin Selection Rules, are therefore considered "allowed" transitions. Alternatively, an excited singlet state electron (S₁) can undergo spin inversion and populate the lower-energy first excited triplet state (T₁) via intersystem crossing (ISC); a spin-forbidden process, since the spin of the electron is no longer conserved. The excited electron can then undergo a second spin-forbidden inversion and depopulate the excited triplet state (T₁) by decaying to the ground state (S₀) via phosphorescence (T₁ → S₀). Owing to the spin-forbidden triplet to singlet transition, the lifetime of phosphorescence (τ_P = 10⁻³–1 second) is considerably longer than that of fluorescence.^[4]

Photosensitizers and photochemistry

Tetrapyrrolic photosensitizers in the excited singlet state (1Psen*, S₁ > 0) are relatively efficient at intersystem crossing and can consequently have a high triplet-state quantum yield. The longer lifetime of this species is sufficient to allow the excited triplet state photosensitizer to

interact with surrounding bio-molecules, including cell membrane constituents.^[4]

Photochemical reactions

Excited triplet-state photosensitizers can react via Type-I and Type-II processes. Type-I processes can involve the excited singlet or triplet photosensitizer (1Psen*, S₁; 3Psen*, T₁), however due to the short lifetime of the excited singlet state, the photosensitizer can only react if it is intimately associated with a substrate. In both cases the interaction is with readily oxidisable or reducible substrates. Type-II processes involve the direct interaction of the excited triplet photosensitizer (3Psen*, T₁) with molecular oxygen (3O₂, 3Σ_g).^[4]

Type-I processes [edit] Type-I processes can be divided into Type I(i) and Type I(ii). Type I (i) involves the transfer of an electron (oxidation) from a substrate molecule to the excited state photosensitizer (Psen*), generating a photosensitizer radical anion (Psen*⁻) and a substrate radical cation (Subs^{•+}). The majority of the radicals produced from Type-I(i) reactions react instantaneously with molecular oxygen (O₂), generating a mixture of oxygen intermediates. For example, the photosensitizer radical anion can react instantaneously with molecular oxygen (3O₂) to generate a superoxide radical anion (O₂^{•-}), which can go on to produce the highly reactive hydroxyl radical (OH•), initiating a cascade of cytotoxic free radicals; this process is common in the oxidative damage of fatty acids and other lipids.^[4] The Type-I process (ii) involves the transfer of a hydrogen atom (reduction) to the excited state photosensitizer (Psen*). This generates free radicals capable of rapidly reacting with molecular oxygen and creating a complex mixture of reactive oxygen intermediates, including reactive peroxides.^[4]

Type-II processes [edit] Type-II processes involve the direct interaction of the excited triplet state photosensitizer (3Psen*) with ground state molecular oxygen (3O₂, 3Σ_g); a spin allowed transition—the excited state photosensitizer and ground state molecular oxygen are of the same spin state (T).^[4] When the excited photosensitizer collides with molecular oxygen, a process of triplet-triplet annihilation takes place (3Psen* → 1Psen and 3O₂ → 1O₂). This inverts the spin of one oxygen molecule's (3O₂) outermost antibonding electrons, generating two forms of singlet oxygen (1Δ_g and 1Σ_g), while simultaneously depopulating the photosensitizer's excited triplet state (T₁ → S₀). The higher-energy singlet oxygen state (1Σ_g, 157 kJ mol⁻¹ > 3Σ_g) is very short-lived (1Σ_g ≤ 0.33 milliseconds (methanol), undetectable in H₂O/D₂O) and rapidly relaxes to the lower-energy excited state (1Δ_g, 94 kJ mol⁻¹ > 3Σ_g). It is, therefore, this lower-energy form of singlet oxygen (1Δ_g) that is implicated in cell injury and cell death.^[4]

4. Conclusion

Immunotherapies represent the most important and transformative classes of new and emerging cancer treatments, as these treatments can lead to prolonged disease-free survival for some cancers that respond poorly to conventional treatments. Although many new and

emerging cancer therapies are improving survival, their longterm and late-onset effects are poorly understood. Some newer treatment approaches are focused on reducing or correcting the toxicity and morbidity of standard treatments (e.g., reduction in the extent of axillary surgery, less invasive surgical procedures, or use of proton radiation therapy). In time, these may become standard of care as their effectiveness and safety become more evident National Academies of Sciences, Engineering, and Medicine. 2021. *Diagnosing and Treating Adult Cancers and Associated Impairments*. Washington, DC: The National Academies Press. Human genomic, transcriptional, proteomic, and epigenetic information has never been more accessible than now thanks to advances in medical sciences and electronics. Since every patient's TME is unique, a single CRC treatment strategy was never an option. Moreover, individualized therapeutic approaches are required due to tissue heterogeneity. Although conventional cytotoxic drugs are always the first line of treatment for solid tumors, drug resistance causes patients to develop incurable recurring CRC. As a result of these shortcomings, the development of novel approaches with significant benefits and minimal drawbacks as future perspectives is required. Radiotherapy is also a promising option for rectal cancer patients. But, it has some plausible and long-term toxicity effects on vital organs that must be overcome by modifying radiation intensities

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