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BIOCHEMICAL PATHWAYS AND METABOLITES IN CANCER-ANTICANCER INTERACTION: A REVIEW

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Abstract

Cancer-related chemotherapeutics research and biochemical foundations are closely intertwined. Many chemotherapeutics exert their effects by targeting regulatory enzymes, metabolic intermediates, molecular processes, or immune-related pathways involved in cell growth and proliferation. This review examines the historical development of chemotherapeutics, from the initial use of nitrogen mustard to the advent of biological therapies. Folate antagonists, for instance, inhibit enzymes necessary for DNA synthesis. Cisplatin induces tumor cell apoptosis by crosslinking DNA bases, thereby disrupting DNA repair mechanisms. Rituximab, an anti-CD20 monoclonal antibody used to treat follicular B-cell non-Hodgkin lymphoma, operates through complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity. The study of chemotherapeutics' biological roles and mechanisms has consistently emphasized the biochemical interactions with regulatory enzymes, metabolic intermediates, molecular processes, and immune pathways during cell growth and proliferation. This review underscores the integral role of biochemical research in the evolution and effectiveness of cancer therapies.

INTRODUCTION

Abbreviations: Akt: A type of serine/threonine protein kinase. Also called protein kinase B; ALL: Acute lymphoblastic leukemia; ALK: Anaplastic lymphoma kinase; Bcl-2: B-cell lymphoma 2; Bcl-XL: B-cell lymphoma-extra large; BRCA1: Breast cancer gene 1; BRCA2: Breast cancer gene 2; CYP: Cytochrome P450; EGFR: Epidermal growth factor receptor; GPX4: Glutathione peroxidase 4; HER-2: Human epidermal growth factor receptor 2; HSP90: Heat shock protein 90; NSCLC: Non-small cell lung cancer; NTRK: Neurotrophic receptor tyrosine kinase; PARP: Poly (ADP-ribose) polymerase; PD-1: Programmed death-1; RRM2: Ribonucleotide Reductase Regulatory Subunit M2; STAT3: Signal transducer and activators of transcription; Trk: Tropomyosin receptor kinase; 5-FU: 5-fluorouracil.

Background

Many historical records revealed that cancer was found before human existence on the earth evidenced by some bone tumors that were discovered in prehistoric animals' traces and fossils [1]. For the time being, cancer is one of the fatal diseases hence it is an

imposing motif for research to develop new drugs against cancerous cells [2]. According to the cancer report declared by the World Health Organization in 2014, cancer gave rise to more than 8 million deaths worldwide in 2012, nearly 10 million deaths in 2020 or one-sixth of each death, and the figure is predicted to ascend to 22 million by 2035 [3,4]. In 2020, the figures and the most common cancer death causes were 2.26 million cases due to breast cancer, 2.21 million cases due to lung cancer, 1.93 million cases due to colorectal cancer, 1.41 million cases due to prostate cancer, 1.20 million cases due to non-melanoma skin cancer, and 1.09 million cases due to gastric carcinoma [4].

Although chemotherapeutics is the most frequently used treatment for quelling the proliferation of cancerous cells, their surrounding environments, and metastasis as well as disease progression, chemotherapy not only deadens proliferating cancer cells but inescapably hit normal cells as well, giving rise to many adverse effects. Therefore, new antitumor medications with maximal efficacy and fewer adverse effects are imperatively required [5-7]. Cytotoxic chemotherapy is progressively being replenished by a new promising generation of medications that aim to recognize specific targets inside or on the surface of tumor cells, and research on adverse effects and resistance to antitumor drugs are continuously running [8]. In this context, sophisticated clinical trials adopting a combination of new agents with classic ones are implemented to expand and improve treatment options and overall survival [9]. An emerging breakthrough pointed to the critical role of biochemical and metabolic alterations in carcinogenesis though most of the researchers in this field were focusing on characterization/identification of genetic lesions [10]. This review aims to highlight the historical role of some metabolites and chemical/biochemical intermediates utilized in some chemotherapeutics' genesis as shown in Figure 1.

Nitrogen Mustard

In 1942, the era of chemotherapy had begun with the first use of nitrogen mustards in the treatment of non- Hodgkin's lymphoma [11]. Goodman and Gilman set up an animal model by creating lymphomas in mice and reported that nitrogen mustards could be employed for the treatment of lymphoma. Then, Lindskog, a chest surgeon, in collaboration with the pre-mentioned researchers injected mustine into non-Hodgkin's lymphoma patient and noticed a spectacular regression in his tumor mass. This finding was the first recognition that tumors could be fought by chemotherapeutics although the effect of mustine lasted just for little weeks [12-14].

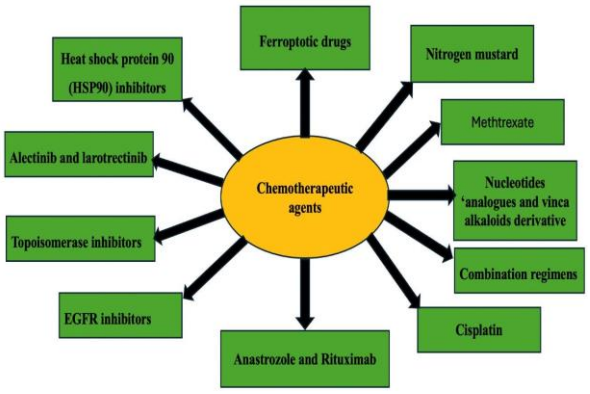

Figure 1: Different metabolites and chemical/biochemical intermediates utilized in some chemotherapeutics' genesis.

Mustard gas and nitrogen mustard were the oldest chemotherapeutics that were utilized as early forms of DNA inter-strand cross-linking agents [15]. Mustard binds to target cell surface receptors, activates intracellular reactive oxygen and nitrogen species enhancing the production of peroxy-nitrite ($ONOO^-$) that, in turn, causes damages to some organic molecules including DNA, lipids, and proteins. This led to the activation of poly (ADP-ribose) polymerase (PARP) [16].

Methotrexate

Nearly after the second World War, Farber, a pathologist, began the next approach to chemotherapeutics against cancer. He found that Acute Lymphoblastic Leukemia (ALL) cells proliferation seems to be enhanced by folic

acid (vitamin B9). Upon his notice, antifolates or folate analogues namely aminopterin and then amethopterine (methotrexate), synthesized by Lederle Laboratories, were given to the children with ALL in 1948. These folate antagonists could block folate-requiring enzymes needed for DNA formation and hence induction of remission in children with ALL. Although the principle of action was clear, remissions were abridged but could restore normal bone-marrow function [17,18].

Being an antimetabolite, methotrexate inhibits the enzyme dihydrofolate reductase which transforms dihydrofolate to tetrahydrofolate, involved in purines and thymidylate synthesis, and therefore suppresses nucleic acid biosynthesis [19].

Nucleotides 'Analogues and Vinca Alkaloids Derivative

In 1951, Wright et al showed that methotrexate could be utilized in remission of breast cancer and hence in the treatment of solid tumors [20]. Then, many purine analogues were inspected by Joseph Burchenal, leading to the discovery of a highly efficient antileukemic drug, 6-mercaptopurine. Later, the anticancerous effect of the vincristine or oncovin (vinca alkaloids derivative) was revealed to be due to their ability to target microtubule engaging the spindle checkpoint and arresting S-phase and hence cell cycle progression in mitosis [21,22]. Cytochrome P450 3A5 (CYP3A5) is 9- to 14-fold more active in the metabolism of vincristine than cytochrome P450 3A4 (CYP3A4). Some recent results indicated that dimethylurea when added at the C20' position in vincristine may raise its binding affinity and result in promoted interactions with the less polymorphic CYP3A4 rather than CYP3A5 [23].

In the middle 1950s, Heidelberger et al, attached a fluorine atom to the pyrimidine base, uracil, at C5 to synthesize 5-fluorouracil (5-FU) which inhibits thymidylate synthase. By doing this, they tried to target a unique biochemical finding in rat hepatoma metabolism, in which, there was relatively higher uptake and utilization of uracil in tumor cells compared to normal tissue [24].

Combination Regimens

It is classified as a breakthrough in cancer therapy that occurred in 1965. Cancer cells could certainly mutate to turn out to be resistant to an individual chemotherapeutic drug, yet by giving various drugs concurrently it might be more difficult for the growth to develop such capacity to the combination [25]. The approach of multiple chemotherapeutics was expanded by DeVita and Canellos, in 1963, who presented MOPP (Nitrogen mustard, Vincristine, Prednisolone, and Procarbazine) regimen for the treatment of lymphoma. In this context, Holland et al offered what so-called POMP (Prednisolone, Vincristine, Methotrexate, and 6-Mercaptopurine) regimen for the treatment of ALL in children. Hence, the ability of combined chemotherapeutics to recuperate advanced Hodgkin's lymphoma and acute childhood leukemia removed the predominating view of pessimism about the anti-tumor drugs [26,27].

Vincristine suppresses mitosis at the metaphase by disrupting mitotic spindle formation particularly during the M and S phase of cell cycle [28].

Cisplatin

In 1968, Rosenberg *et al*. reported that cisplatin when implemented intraperitoneally with nonlethal dose of 8 mg/kg to mice, caused marked tumor regression of sarcoma and leukaemia [29]. Cisplatin (*cis*-diamminedichloroplatinum) is efficiently used for treatment of different types of cancers, such as germ cell tumors, lymphomas, carcinomas, and sarcomas. The mechanism of action descends from its capability to crosslink with the DNA guanine and, to a lesser extent, adenine bases; interception with the DNA repair mechanisms, giving rise to cause DNA damage, and induction of apoptosis in tumor cells [30,31]. Since that time, the conception of oncology has not existed till 1973 when the technology of medical oncology was initiated internal medicine as a sub-specialty field [27].

In 2008, Some researchers reported that the induction of apoptosis by cisplatin on human colon cancer cells depends on the mitochondrial serine-protease [32,33].

Cisplatin induces its anticancerous and cytotoxic properties via linking to the nuclear DNA with subsequent intervention of the normal DNA replication and/or transcription mechanisms which eventually leads to cell death. In addition, there is strong evidence proposing that the cytotoxic effects of cisplatin are induced by binding of this drug to non-DNA targets, typical proteins. to initiate its cytotoxic biochemical action [34].

Anastrozole and Rituximab

Less than one-tenth of the chemotherapeutics, that entered clinical trials, had been approved by the FDA in the period from 1970 to 1990 [35]. In 1994 and 1995, The tumor suppressor genes BRCA1 and BRCA2 were respectively cloned. These genes were found to increase the risks of ovarian and breast cancer in ladies and the risks of several other tumors in both genders [36]. In 1996, the FDA was approved anastrozole to be used in the treatment of estrogen receptor-positive in the advanced breast cancer in post-menopausal women. Since estrogens are fundamental in the emergence of breast cancers in both types pre- and postmenopausal women, anastrozole, an inhibitor of estrogen synthesis, is the first aromatase blocker to be ratified as a chemotherapeutic [36,37]. Rituximab was approved by the FDA in 1997 for the treatment of follicular B-cell non-Hodgkin lymphoma. This drug is an anti-CD20 monoclonal antibody that affects complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity leading to cellular structural changes and apoptosis [36,38]. One year later, Trastuzumab, another monoclonal antibody, had been approved for the treatment of HER2-positive early-stage breast cancer by targeting HER2 (known as a transmembrane tyrosine- kinase receptor that goes to the group of the epidermal growth factor receptor called EGFR), inducing an immune-mediated reaction that leads to downregulation and internalization of HER2 [39,40]. Trastuzumab had been chemically conjugated with mertansine, a cytotoxic agent, to form the immunotoxin ado-trastuzumab emtansine (T-DM1) which had been approved by FDA in 2013 for treatment of HER2-positive breast cancer [36].

EGFR Inhibitors

Tumour growth, including cell proliferation, progression, and inhibition of apoptosis, had been found to be entangled with activation of Epidermal Growth Factor Receptor (EGFR). Thus, compounds that inhibit the epidermal growth factor receptor would have remarkable evidence of anti-cancer efficacy. Of these compounds, Gefitinib had been approved by FDA in 2003. It competitively inhibits the function of ATP-binding of the tyrosine kinase catalytic site of EGFR and hence could be used as a chemotherapeutic in metastatic or advanced carcinoma of the lung with non-small-cell [41-43].

In 2003, bortezomib had been introduced for the treatment of multiple myeloma. The boron atom in bortezomib binds the catalytic site of the 26S proteasome which regulates protein expression and function by degradation of ubiquitylated proteins, and also rids the cell of abnormal or misfolded proteins. Another important mechanism of bortezomib action is related to its capability to upregulate a proapoptotic protein called NOXA that can interact with the anti-apoptotic proteins of Bcl-2 subfamily Bcl-XL and Bcl-2, leading to apoptosis and cell death in tumor cells [44-46].

Topoisomerase Inhibitors

Topoisomerase inhibitors have been widely used as anticancer drugs for the last 2 decades [47]. DNA topoisomerase activity can be inhibited by a large number of plants' secondary metabolites like polyphenols, terpenoids, alkaloids, and quinones These metabolites can be used as natural anticancer drugs. DNA topoisomerases are essential cellular enzymes for different DNA metabolic processes such as transcription, replication, recombination. These enzymes alter the supercoiling and topological state of DNA through breaking, passing a segment and sealing of the DNA strands [48,49].

Many researchers had focused on ribonucleotide reductase inhibitors as

promising chemotherapy for hematologic cancers. Their mechanism of action occurs by inhibiting the rate-limiting enzyme, ribonucleotide stenography which catalyses the reduction of ribonucleotides to deoxyribonucleotides, in DNA synthesis and repair. Examples for this category are hydroxyurea, fludarabine, cladribine, and gemcitabine, which inhibit ribonucleotide reductase by different mechanisms like inhibiting ribonucleotide reductase activity by direct regulation of RRM2 acetylation in cancer cells [50-52]. Fludarabine had been approved by FDA in 2008 [53].

Alectinib and Larotrectinib

By the end of 2015, the FDA approved alectinib (alecensa) for the treatment of metastatic Non-Small Cell Lung Cancer (NSCLC) and Anaplastic Lymphoma Kinase (ALK)-positive. It is known as a kinase inhibitor that acts through inhibiting ALK phosphorylation and ALK-mediated activation of the downstream signalling proteins STAT3 and AKT. Since carcinogenesis could be halted by cytotoxic T cells or what so called tumor-specific CD8+T cells that functionally declined by the Programmed Death-1 (PD-1). PD-1 is therefore considered as a negative regulator indicator of T cell function [54,55]. Abdelhamed *et al.* (2016) spotlighted the importance of AKT-STAT3 pathway as a propitious target for the potentiation of anti-tumor immune responses by the regulation of PD-L1 expression on cancer cells [55]. In 2018, the FDA approved larotrectinib (Vitrakvi) for treatment of paediatric and adult patients with solid tumors that have a Neurotrophic Receptor Tyrosine Kinase (NTRK) gene fusion. Larotrectinib ($C_{21}H_{22}F_2N_6O_2$) is an inhibitor of tropomyosin kinase receptors TrkA, TrkB, and TrkC [56].

Heat Shock Protein 90 (HSP90) Inhibitors

Heat Shock Protein 90 (HSP90) is typically 90 kDa chaperone protein that is taking charge of folding, stabilizing, and activating many client proteins embroiled in DNA repair, control of cell cycle and signal transduction. Since hundreds of oncoproteins are represented as client proteins for HSP906–8, HSP90 could be considered as a central target in different cancers pathogenicity. Being as a second generation HSP90, luminespib (LUM)which was co-developed by the UK Institute of Cancer Research, LUM had displayed antitumor potential in several tumor either in combination with other chemotherapeutics or alone. Although it had partial response and led to stable disease, particularly Non-Small Cell Lung Cancer (NSCLC), it unsuccessfully did not pass the endpoints of clinical trials [57].

Ferroptotic Drugs

A novel approach in cancer treatment was recently suggested that utilizing the mechanism of iron-dependent, non-apoptotic cell death, the so-called ferroptosis, could have promising therapeutic advantages of triggering this sort of cell death. Several studies have specified that apoptotic mechanisms are often suppressed in resistant cells, resulting in therapeutic drug unsuccessfulness. Therefore, promotion of cell death is nowadays requiring new alternative plans and strategies. There is a strong evidence that chemotherapeutic-resistant tumor cells are typically susceptible to ferroptosis since cancer cells engorge higher quantities of iron compared with healthy cells [58]. Examples of some studied ferroptotic drugs include ironomycin (salinomycin), cisplatin, lanperisone, acetaminophen, sulfasalazine, ferumoxytol, sorafenib, fenugreek (trigonelline), artesunate, and combination of siramesine and lapatinib. These drugs enhance ferroptosis which is regarded as a sort regulated cell death by provoking oxidative intracellular microenvironment disturbances under the fundamental regulatory role of glutathione peroxidase 4 (GPX4) [59].

Conclusion

Most of oncological and pharmacological studies on the structure, mode of action, and biological role of chemotherapeutics never neglected the biochemical evidence shared either by intervention with regulatory enzymes, some metabolic intermediates, molecular processes, or immune-related

pathways during cell growth and proliferation. In this context, methotrexate supresses the enzyme dihydrofolate reductase which transforms dihydrofolate to tetrahydrofolate, involved in purines and thymidylate synthesis. 5-fluorouracil is an antimetabolite that inhibits thymidylate synthase. Cisplatin interferes with the normal DNA replication and/or transcription by linking to the nuclear DNA. Whereas, alectinib is a kinase inhibitor that acts via inhibiting ALK phosphorylation and ALK-mediated activation of the downstream signalling proteins STAT3 and AKT, and larotrectinib is an inhibitor of tropomyosin kinase receptors.

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