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Review

Cancer metabolism and oxidative stress: Insights into carcinogenesis and chemotherapy via the non-dihydrofolate reductase effects of methotrexate

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ABSTRACT

Methotrexate has been in use as an anti-cancer agent for over 60 years. Though inhibition of dihydrofolate reductase is its best known mechanisms of action, its non-dihydrofolate reductase dependent mechanisms disrupt metabolic pathways resulting in a depletion of NAD(P)H and increasing oxidative stress. These mechanisms highlight a novel dependence of cancer cells on their metabolic abnormalities to buffer oxidative stress and chemotherapeutic agents interfere with these cellular abilities. Mitochondria appear to play a significant role in maintaining cancer cell viability and alterations in metabolism seen in cancer cells aid this mitochondrial ability. Further research is needed to understand the effects of other chemotherapeutic agents on these pathways.

Contents

1. Introduction

The origins of modern day chemotherapy can be traced back to the early days of World War II. On December 2, 1943, the port of Bari, Italy was the target of a German air raid on Allied forces [1–3]. The casualties of this air raid far outnumbered those expected for the size of the attack. Though banned by the Geneva Protocol of 1925, Allied forces were concerned with the possibility that the German army would resort to the use of chemical weapons. In August of 1943, President Roosevelt approved the shipment of a secret cargo of mustard gas via SS Harvey. The explosion of the ship during this raid released its contents onto the city inflicting an untold number of civilian casualties. With some variation in details depending on the source, investigations by Dr. Stewart Francis Alexander, a Lieutenant Colonel and expert in chemical warfare noted significant suppression of both lymphoid and myeloid tissues in those exposed to the chemical agent [1]. Later research with a related compound, mustine, led to successful reduction of tumor mass in a patient with non-Hodgkin's lymphoma and to a realization that pharmacotherapy of cancers was feasible.

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Following World War II, a second step forward in chemotherapy was made by a pathologist at Harvard Medical School. Sidney Farber had studied the stimulating effect of folic acid on the proliferation of acute lymphoblastic leukemia cells when given to children with this cancer [4]. At that time, knowledge of the role of folic acid was limited to its effect as a cofactor in the synthesis of purines. This observation led to one of the first attempts at rational drug design. In collaboration with the first chemists to successfully synthesize folic acid at Lederle Laboratories, Farber helped design the folate analog aminopterin [4,3]. Later, this collaboration led to the synthesis of the antibiotic trimethoprim and the chemotherapeutic agent amethopterin, more famously known as methotrexate [4]. Since that time, the intracellular biochemistries of both folic acid and methotrexate have been further explored and detailed.

The classically taught mechanism of action for methotrexate is inhibition of dihydrofolate reductase (DHFR) to deplete cellular pools of tetrahydrofolate and stop the production of thymidylate. Cells lacking adequate thymidine are unable to synthesize DNA, which results in the arrest of cellular proliferation. The combined effect is thought to lead to the demise of rapidly dividing cell populations either through apoptosis or autophagy. In cancer therapy, sustained maximal DHFR inhibition is targeted and important for several reasons. First, it provides steady inhibition of DNA synthesis, and, second, it minimizes the risk of developing resistance to MTX [5]. With only 1% of the average cellular DHFR concentration required to maintain a sufficient reserve of reduced folate coenzymes, high doses of MTX are required to achieve this effect and are frequently limited by toxicities [6]. Major adverse effects of MTX therapy include dermatitis, elevated transaminases, mucositis, and myelosuppression. Leucovorin, a folate derivative that bypasses the DHFR reaction, is used as a rescue agent to curb the incidence and severity of these effects and often found in high dose MTX protocols (see Fig. 1).

The in vitro mechanics of the anti-folate MTX on DHFR are well known. Newer studies reveal in vivo biochemical interactions of MTX with multiple enzymes. They describe interactions of MTX with multiple metabolic pathways ranging from cellular energy production, antioxidant regeneration, nucleotide synthesis and buffering of oxidative stress [7,8,6]. This review will describe the peculiarities of cancer metabolism and the non-DHFR mechanisms of MTX. These interactions support the hypothesis that mitochondria and this organelle's function in buffering of oxidative stress. In addition to dysfunctional glycolysis, this mitochondrial function appears to have a significant influence on the cancer cell's metabolism and the mechanisms of other chemotherapeutic agents.

2. Methods

Online literature searches of PubMed and Google Scholar were performed using the following terms and related biochemical pathways: autophagy, aerobic glycolysis, cancer metabolism, hydrogenosomes, glutamine metabolism, methotrexate, mitophagy, oxidative stress and cellular redox balance. No limitations were placed on the date of publication. Though the number of search results was not recorded, approximately 1800 publications were reviewed. The types of manuscripts included reviews, original research and letters to editor with both clinical and pre-clinical data. Historical texts and materials were reviewed in order to provide insight into the origins of chemotherapeutic agents.

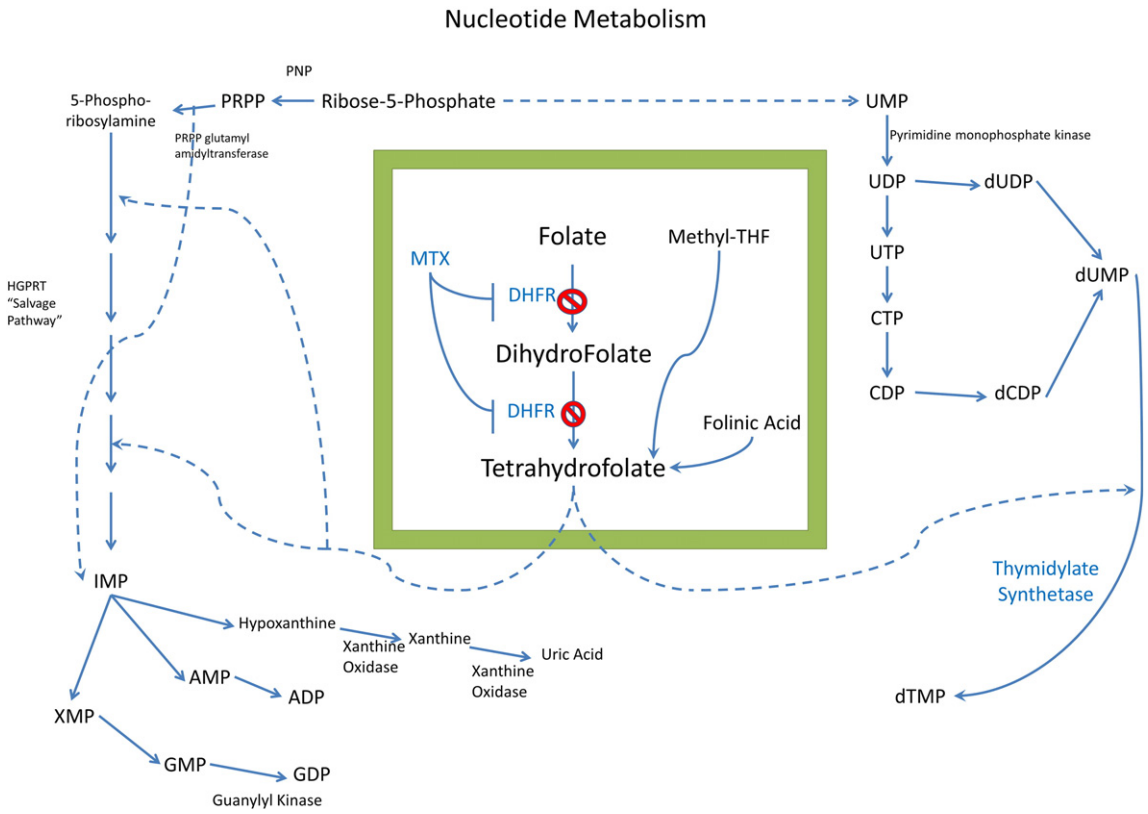

Fig. 1. Effects of methotrexate on folate metabolism in relation to nucleotide metabolism. Via its inhibition of dihydrofolate reductase, methotrexate interferes with the generation of tetrahydrofolate and subsequently, DNA synthesis. Tetrahydrofolate is metabolized further for use as a cofactor in the synthesis of dTMP. Folinic acid, leucovorin, is often used to rescue cells from methotrexate and restore cellular stores of tetrahydrofolate. In addition to interference with DNA synthesis, this diagram superficially shows the involvement of tetrahydrofolate in the metabolism of purines. Legend: ADP, adenosine diphosphate; AMP, adenosine monophosphate; CDP, cytidine diphosphate; CTP, cytidine triphosphate; dCDP, deoxycytidine diphosphate; DHFR, dihydrofolate reductase; dTMP, deoxythimidine monophosphate; dUDP, deoxyuridine diphosphate; dUMP, deoxyuridine monophosphate; GDP, guanine diphosphate; GMP, guanine monophosphate; HGPRT, hypoxanthine-guanine phosphoribosyltransferase; IMP, inosine monophosphate; Methyl THF, methyltetrahydrofolate; MTX, methotrexate; PNP, purine nucleotide phosphorylase; PRPP, phosphoribosyl pyrophosphate; UDP, uracil diphosphate; UMP, uracil monophosphate; UTP, uracil triphosphate; XMP, xanthine monophosphate.