Biochimica et Biophysica Acta 1830 (2013) 3350–3353

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

Review

Glutathione and glutathione analogues; Therapeutic potentials ☆

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ARTICLE INFO

Article history:
Received 24 September 2012
Received in revised form 2 November 2012
Accepted 19 November 2012
Available online 28 November 2012

Keywords:
Glutathione
Cytoprotection
Chemosensitivity

ABSTRACT

Background: Glutathione (GSH) and related enzymes are critical to cell protection from toxins, both endogenous and environmental, including a number of anti-cancer cytotoxic agents.
Scope of review: Enhancing GSH and associated enzymes represents a longtime and persistent aim in the search for cytoprotective strategies against cancer, neurologic degeneration, pulmonary and inflammatory conditions, as well as cardiovascular ailments. The challenge is to identify effective GSH analogues or precursors that generate mimic molecules with glutathione's cellular protective effects. This review will provide an update on these efforts. Much effort has also been directed at depleting cellular GSH and related cytoprotective effects, in order to sensitize established tumors to the cytotoxic effects of anti-cancer agents. Efforts to deplete GSH have been limited by the challenge of selectivity doing so in tumor and not in normal tissue so as to avoid enhancing the toxicity of anti-cancer drugs. This review will also provide an update of efforts at overcoming the challenge of targeting the desired GSH depletion to tumor cells.
Major conclusions: This chapter provides a brief background and update of progress in the development and use of GSH analogues in the therapeutic setting, including the pharmacological aspects of these compounds.
General significance: This is an area of enormous research activity, and major advances promise the advent of novel therapeutic opportunities in the near future.
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1. Introduction

The modulation of cellular glutathione (GSH) is a double-edged sword, both sides of which have been exploited for potential therapeutic benefit. Enhancing the capacity of GSH, and its associated enzymes, to protect cells from redox-related perturbations or environmental toxins represents a longtime and persistent aim for those searching for cytoprotective approaches to prevention of cancer, neurologic degeneration, pulmonary and inflammatory conditions, as well as cardiovascular ailments [1–3]. Efforts to increase cellular GSH levels by the direct administration of reduced glutathione face limitations by solubility, absorption and stability [4]. This has resulted in a significant effort to identify GSH analogues or precursors, or to generate mimic molecules with the capacity to reduce oxygen radical and peroxidation related effects on cells.

Glutathione is an important intracellular antioxidant and redox potential regulator that plays a vital role in drug detoxification and elimination and in cellular protection from damage by free radicals, peroxides, and toxins. Molecular alterations reported in many of the components of the glutathione system in various tumors and cancer cell lines can lead to an increased cell survival and enhanced chemotherapy drug resistance. Therefore, much effort has been directed at depleting cellular GSH and related cytoprotective effects in order to sensitize established tumors to the cytotoxic effects of anti-cancer agents. One of the earlier approaches was inhibition of glutathione synthesis, by blocking the rate-limiting step of gamma-glutamylcysteine synthesis (GCS). Using the molecule buthionine sulfoximine (BSO), we performed the earliest clinical trials, and did indeed demonstrate depletion of glutathione in clinical specimens [5]. However, the approach was limited by availability of BSO, and more importantly, by its lack of selectivity for tumor *versus* normal tissue; some normal cells were also sensitized by GSH depletion to cytotoxic chemotherapy. However, the recognition that some tumors relied on elements of the GSH-related cytoprotective detoxification system did generate another approach, which is aligned with the search for GSH analogues as above, but uses them to competitively inhibit detoxification enzymes such as glutathione S-transferase (GST), as a means of chemosensitization, which is discussed below.

This chapter will provide a brief background and update of progress in the development and use of GSH analogues in the therapeutic setting, including pharmacological aspects of these compounds.

2. Scope of the review

2.1. Increasing glutathione

Given the range of critical cellular functions involving GSH, it has long been considered that increasing GSH would be cytoprotective. Indeed, recent studies suggest a role in protecting neuronal tissue,

☆ This article is part of a Special Issue entitled Cellular functions of glutathione.
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http://dx.doi.org/10.1016/j.bbagen.2012.11.016

pulmonary cells and cardiovascular structures by enhancing GSH-related detoxification capacity [1–3]. However, since GSH cannot be administered directly, the creative notion of precursors was the subject of multiple efforts. The early focus was on cysteine, although it too could not be delivered directly due to toxic effects [6]. This quite naturally led to the generation of analogues.

An early version was N-Acetyl Cysteine (Mucomyst) (Fig. 1), which had a proven role in specific clinical settings, including in the treatment of Cystic Fibrosis lung and of hepatitis induced by acetaminophen overdose [7]. However pharmacologic and other factors have limited the study of NAC beyond these few indications.

In the 1990s, we and others showed that L-2-oxothiazolidine-4-carboxylic acid (OTC) (Fig. 1), a 5-oxo-L-proline analogue that is metabolized by 5-oxoprolinase, not only increased GSH in normal bone marrow cells, and protected mouse bone marrow from cytotoxic chemotherapy-induced suppression, but most remarkably it also selectively depleted GSH in xenograft human tumors [8]. While never fully confirmed, we proposed that this effect resulted from differential expression of the enzyme 5-oxoprolinase in tumor *versus* normal host tissue [9].

Although neither of these early approaches was successfully developed clinically, others continued to pursue the strategy of generating GSH analogues and synthetic molecules with GSH-like activity with respect to redox function [10]. Variations on the GSH molecule designed to enhance its stability and uptake by cells showed promise. YM737 (N-(N-gamma-L-glutamyl-L-cysteine) glycine L-isopropyl ester sulfate monohydrate) (Fig. 1), a monoester of glutathione, was actually favorably compared to N-acetyl-L-cysteine in a study of hypoxia/hypoglycemia-induced decreases in CA1 presynaptic fiber spikes and 2-deoxyglucose uptake [11]. It was also shown to have beneficial effect in a rat cerebral ischemia model [12].

One approach is the cyclization of GSH in order to stabilize it from the effects of various degradative enzymes, and these molecules do appear to have anti-tumor activity [13]. Other investigators generated a library of tetrapeptic GSH analogues referred to as UPF peptides [14]. Here an O-methyl-L-tyrosine is added to the N-terminus of glutathione, based on the reasoning that methoxy groups are responsible for antioxidant activities in molecules such as melatonin. These UPF1 compounds appear to have a potent anti-oxidant activity, and in particular to provide significant protection from global cerebral ischemia in *in vivo* models, and in an isolated heart model.

Some have targeted GSH and glutathione transferase-related metabolism by a pro-drug, not to inhibit GST or deplete GSH as seen in examples below, but simply because this metabolic reaction results in a cytotoxic chemical of potential anti-cancer therapeutic value. Another GSH analogue approach is cysteine-substituted S-nitrosoglutathione [15]. Examples are nitric oxide (NO) prodrugs such as O(2)-(2,4-dinitrophenyl) 1-[(4-ethoxycarbonyl)piperazin-1-yl]diazen-1-ium-1,2-diolate (JS-K), which release cytotoxic nitric oxide from the pro-drug (*e.g.* JS-K) as a result of a nucleophilic aromatic substitution by glutathione (GSH) catalyzed by glutathione S-transferase (GST) to form a diazeniumdiolate anion that spontaneously releases nitric oxide (NO). Interestingly, since S-nitrosoglutathione occurs naturally, the converse side of the GSH story is being played out as well. N6022 (Fig. 1) is a novel drug with potent inhibitory activity against S-nitrosoglutathione reductase (GSNOR), an enzyme important in the metabolism of S-nitrosoglutathione (GSNO) and in the maintenance of NO homeostasis. This compound has shown safety and efficacy in animal models of asthma, chronic obstructive pulmonary disease, and inflammatory bowel disease, and is currently in early phase clinical studies in humans [16].

In another approach to enhance cellular detoxification capacity, we have generated novel small molecules that specifically increase cellular levels of the transcription factor Nrf2, which regulates not only GSH synthetic enzymes, but also a variety of other components of a cytoprotective program [17]. These molecules are active in cell lines and remain to be studied in *in vivo* models.

2.2. Decreasing GSH-related detoxification

Once it was recognized that elements of the cytoprotective program are increased in the course of malignant transformation, and that these also render cells resistance to some cytotoxic chemotherapy, the strategy of depleting GSH and related detoxification pathways was generated with the goal of sensitizing cancer cells to chemotherapy, so-called 'chemo sensitization' [18].

Among the earliest such efforts was l-buthionine-(S,R)-sulfoximine (BSO) as mentioned above, an amino acid analogue that functions as a

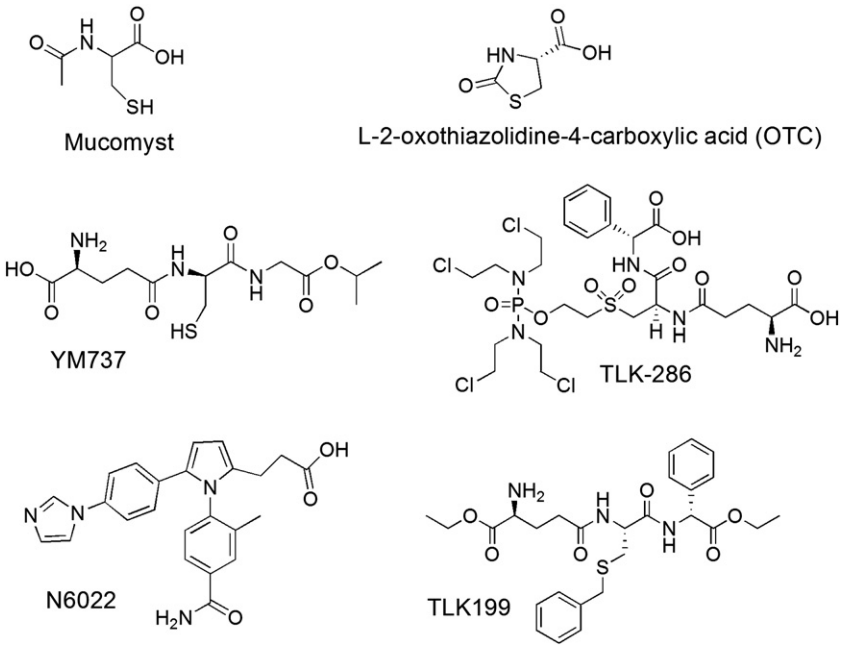

Fig. 1. Chemical structures of glutathione modulators and N6022.

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