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Mini-review

D-penicillamine and other low molecular weight thiols: Review of anticancer effects and related mechanisms

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ABSTRACT

Low molecular weight thiols (LMWTs) like N-acetyl cysteine, D-penicillamine, captopril, Disulfiram and Amifostine, etc. have been used as chemo-preventive agents. Recent studies have reported cell growth inhibition and cytotoxicity in several different types of cancer cells following treatment with several LMWTs. Cytotoxic and cytostatic effects of LMWTs may involve interaction of the thiol group with cellular lipids, proteins, intermediates or enzymes. Some of the mechanisms that have been proposed include a p53 mediated apoptosis, thiyl radical induced DNA damage, membrane damage through lipid peroxidation, anti-angiogenic effects induced by inhibition of matrix metalloproteinase enzymes and angiostatin generation. LMWTs are strong chelators of transition metals like copper, nickel, zinc, iron and cobalt and may cause metal co-factor depletion resulting in cytotoxicity. Oxidation of thiol group can also generate cytotoxic reactive oxygen species (ROS).

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1. Introduction

Low molecular weight thiols (LMWTs) such as N-acetyl cysteine (NAC) have been utilized as adjuvants to chemotherapy due to their free radical scavenging properties, thereby reducing the associated toxicity to normal tissue while increasing the therapeutic index [1–4]. Interestingly, several investigators have reported cytotoxic or cytostatic effects in different types of cancer cells upon treatment with LMWTs [5–8]. The anticancer effects of LMWTs can be described in four distinct categories: (i) Generation of ROS causing direct cellular damage [9,10]. LMWTs elevate intracellular oxidative stress by generating reactive oxygen (ROS) and nitrogen species (RNS) that may cause cytotoxicity [11,12]. The mechanism by which LMWTs generate ROS involves one-electron oxidation of the free thiol group which can be catalyzed by transition metal ions like copper and iron [11,13]. (ii) Inhibition of enzyme activity by chelation of metal co-factors like copper and zinc leading to anti-angiogenesis and extracellular matrix perturbation [14–17]. Copper is an angiogenic cofactor and lowering of elevated serum and tissue copper levels in cancer patients by using LMWTs has been investigated to study anti-angiogenic effects [18–25]. (iii) Modulation of cellular and membrane proteins by thiol disulfide exchange or disulfide formation at cysteine residues [26,27], and (iv) Effect on apoptotic cell signaling pathways [28–30].

LMWTs are strong chelators of transition metal ions like copper and iron and the variation in oxidation potential of the thiol group and type of transition metal ion catalyst have been shown to affect the rate of ROS generation and the cytotoxic dose [31–34].

Some of the LMWTs reviewed in this report are N-acetyl cysteine, captopril, D-penicillamine (D-pen), Tetrathiomolybdate (TM), Disulfiram, Amifostine, Mesna and NOV-002 (Fig. 1).

2. Redox status of normal vs. cancer cells

The cellular redox buffer system is composed of small molecule antioxidants like glutathione (GSH) and enzymatic components including GSH peroxidase, catalase, superoxide dismutase (SOD), peroxiredoxin and thioredoxin [35]. These components together

Abbreviations: ACE, angiotensin converting enzyme; D-pen, D-penicillamine; Dox, doxorubicin; DSF, Disulfiram; DTT, dithiothreitol; ECGF, endothelial cell growth factor; ECM, extracellular matrix; GSH, glutathione; HA, hyaluronic acid; LMWTs, low molecular weight thiols; LPS, lipopolysaccharides; MMP, matrix metalloproteinases; NAC, N-acetyl cysteine; PDTC, pyrrolidine dithiocarbamate; Prx, peroxiredoxin; ROS, reactive oxygen species; RNS, reactive nitrogen species; SOD, superoxide dismutase; TGF, tumor growth factor; TM, Tetrathiomolybdate; tPA, tissue plasminogen activator.

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help maintain a low level of ROS by scavenging reactions that convert ROS to inert compounds [35]. GSH is utilized as a single electron donor in most of the scavenging reactions resulting in its oxidation to GSSG (glutathione disulfide) [13,35] (Fig. 2). The ratio of GSH to GSSG (GSH/GSSG) is often used as a measure of the buffer capacity of a cell, a higher value indicating an improved ability to counter an oxidative insult [36]. Selective perturbation of this balance in cancer cells by increasing the levels of GSSG (NOV-002®) or decreasing the levels of GSH (buthionine sulfoximine and phoron) has been investigated as an anticancer strategy [37–39]. It has been reported that the ratio of GSH/GSSG and the redox buffer capacity of cancer cells are significantly lower than normal cells due to increased metabolic (oxidative) stress [40–44]. This persistent oxidative stress makes them more susceptible to killing by further elevation of intracellular ROS levels [45].

Peroxiredoxin (Prx), catalase, GSH peroxidase play an important role in cellular redox buffer system by neutralizing peroxides generated from superoxide by SOD enzymes. Prx family of enzymes (Prx I–V) are thioredoxin-dependent peroxidases [46,47]. Prx enzymes exist as homodimers and each monomer has a NH_2-terminal conserved cysteine residue that is oxidized by peroxides. This results in disulfide bond formation within the homodimeric species [48]. Thioredoxin family of enzymes reduce the disulfide bond and helps in reactivating Prx [49].

Elevated levels of ROS have the potential to cause cellular damage by oxidizing cellular components (e.g. lipid peroxidation), direct damage to DNA (e.g. strand breaks) or by triggering stress responses leading to apoptotic cell death [50,51]. Comparatively, the redox buffer capacity of normal cells is much greater and they are able to neutralize ROS and prevent any associated damage at similar concentrations [52]. Several studies have shown that LMWTs that act predominantly by ROS elevation have an inherent selectivity towards killing cancer cells. N-acetyl cysteine (NAC) was shown to selectively induce apoptosis in several transformed cell lines with no effect on normal cells [53]. Havre et al. showed that D-pen selectively induced a p53 mediated apoptosis in transformed cells compared to human fibroblasts [5]. Wondrak et al. showed that more than 60% of the murine (B16) and human (A-375, G-361 and LOX) melanoma cells were apoptotic within 24 h of treatment with D-pen whereas no apoptosis induction was seen in primary human skin fibroblasts and epidermal keratinocytes [54,55].

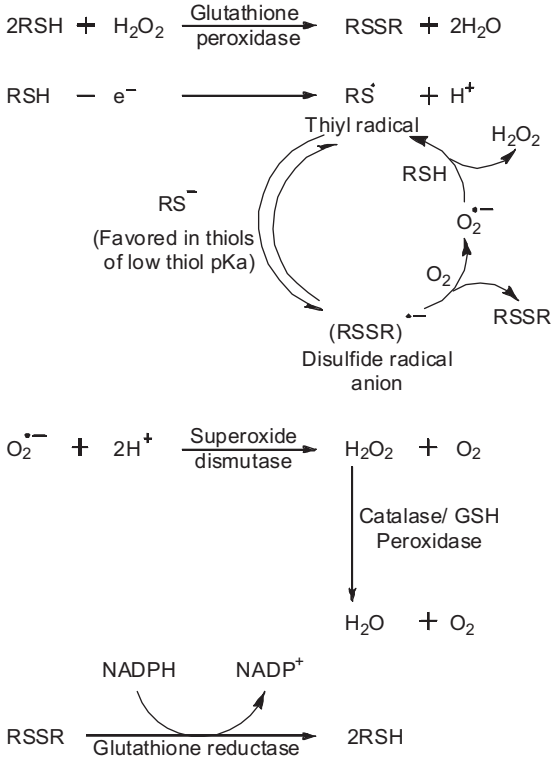

Fig. 2. Pathways of neutralization of reactive oxygen species (ROS) by the cellular redox buffer components. RSH = Low molecular weight thiol (LMWT). Glutathione (GSH) is the predominant intracellular LMWT. RSSR = Symmetrical disulfide of the corresponding LMWT, H_2O_2 = Hydrogen peroxide, O_2^- = Superoxide anion, NADP = Nicotinamide adenine dinucleotide phosphate.

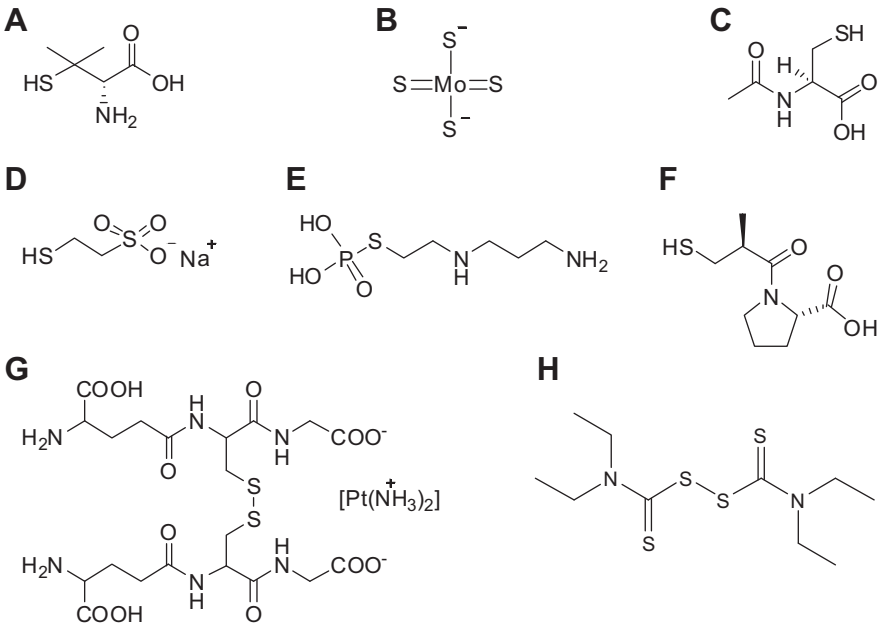

Fig. 1. Chemical structures of some low molecular weight thiols (LMWTs) investigated for their anticancer properties. (A) D-penicillamine (D-pen), (B) Tetrathiomolybdate (TM), (C) N-acetyl cysteine (NAC), (D) Mesna, (E) Amifostine, (F) Captopril, (G) NOV-002 and (H) Disulfiram.

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