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Disulfide-containing parenteral delivery systems and their redox-biological fate

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ABSTRACT

Exploiting the redox-sensitivity of disulfide bonds is an increasingly popular means to trigger drug release at a target location in the body. The bio-reducible linker (containing a disulfide) can be cleaved when the drug delivery system in which it is incorporated passes from the poorly reducing extra-cellular biological environments to the strongly reducing intra-cellular spaces. This phenomenon has been characterized for a variety of drug carriers (*e.g.* antibody–drug conjugates and nucleic acid carriers) and made use of not only for intra-cellular drug release, to provide but also a mechanism of biodegradation. However, successful therapeutic application of redox-sensitive drug delivery systems, which are mostly investigated in the treatment of cancer, depends on timely cleavage of the disulfide in the body. As a result, an accurate and detailed understanding of the biological redox stimulus and the properties of the redox-sensitive moiety is of importance. This review introduces a number of currently relevant reducing agents and redox enzymes, and provides an overview of the redox environments a disulfide-containing drug delivery system encounters upon parenteral administration. Furthermore, the current state of knowledge regarding the behavior and responsiveness of disulfides in these redox-biological compartments is discussed.
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1. Introduction

Disulfides are the most important class of dynamic, redox-responsive covalent bonds found in proteins. The best known functions of these bonds are to guide the precise folding of a protein into its native

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conformation and to stabilize its tertiary and quaternary structures [1,2]. Furthermore, protein disulfides can be used as cellular redox switches, and are involved in signaling processes *via* the transfer of electrons through disulfide cascades [3–5]. Such processes, as well as the thiol–disulfide exchange (Fig. 1) in general, are largely controlled by the redox micro-environment of the biological compartments in which they are located [2,4]. The redox potential of these compartments is maintained by low molecular weight (*e.g.*, glutathione/glutathione disulfide (GSH/GSSG), cysteine/cystine (Cys/CySS)) and macromolecular thiol/disulfide redox couples (*e.g.*, thioredoxin-1 (Trx1), protein disulfide isomerase (PDI)), with different steady-state redox potentials (Fig. 1) [6]. Proteins containing intact disulfide bonds are predominantly found in oxidizing environments such as the extracellular (circulatory) space. In contrast, the cytoplasm and the nucleus are examples of reducing environments in which most proteins are (at least partially) in a reduced form [7].

Due to the naturally occurring difference between the extra- and intra-cellular redox-environments, disulfide bonds are increasingly being examined as responsive linkers for drug delivery systems (DDS). To date, the most advanced and extensively reviewed systems incorporating disulfides are antibody–drug conjugates (ADC) [10–16]. One example of this class is Mylotarg®, which was the first, and thus far remains the sole FDA approved antibody–drug conjugate on the market (but subsequently withdrawn) containing a linker system with a disulfide bond [17]. In addition, several recent reviews have discussed redox responsive gene delivery polyplexes [18–20], liposomes, micelles, nanoparticles, and gels [21–24]. For these diverse systems, the susceptibility of the disulfide bonds to thiol–disulfide exchange is of great importance in determining the therapeutic potential. For the most part, disulfide bonds should be stable in the extra-cellular space and then be exchanged upon exposure to specific reducing cellular compartments. However, a number of factors associated with the DDS itself affect the kinetics of thiol–disulfide exchange [25]. Indeed, steric hindrance and the local electrostatic micro-environment of the disulfide can dramatically alter the responsiveness of the disulfide to biological stimuli [26,27]. This implies that thorough investigation of the specific behavior of disulfide bonds within each DDS is required, including an analysis of the location and extent of disulfide exchange in the complex *in vitro/vivo* settings. Such a detailed picture is necessary not only for understanding the mechanism by which redox-responsiveness can be harnessed for a given DDS, but also for optimizing it.

This contribution provides an overview of the current state of research regarding the redox-biological fate of bio-reducible DDS during their transit through the body. Most of the reported disulfide-containing systems are intended for parenteral administration and investigated in the treatment of cancer. Therefore, this manuscript focuses on the successive redox environments a parenterally administered drug carrier encounters from the blood vessel lumen to the intra-cellular

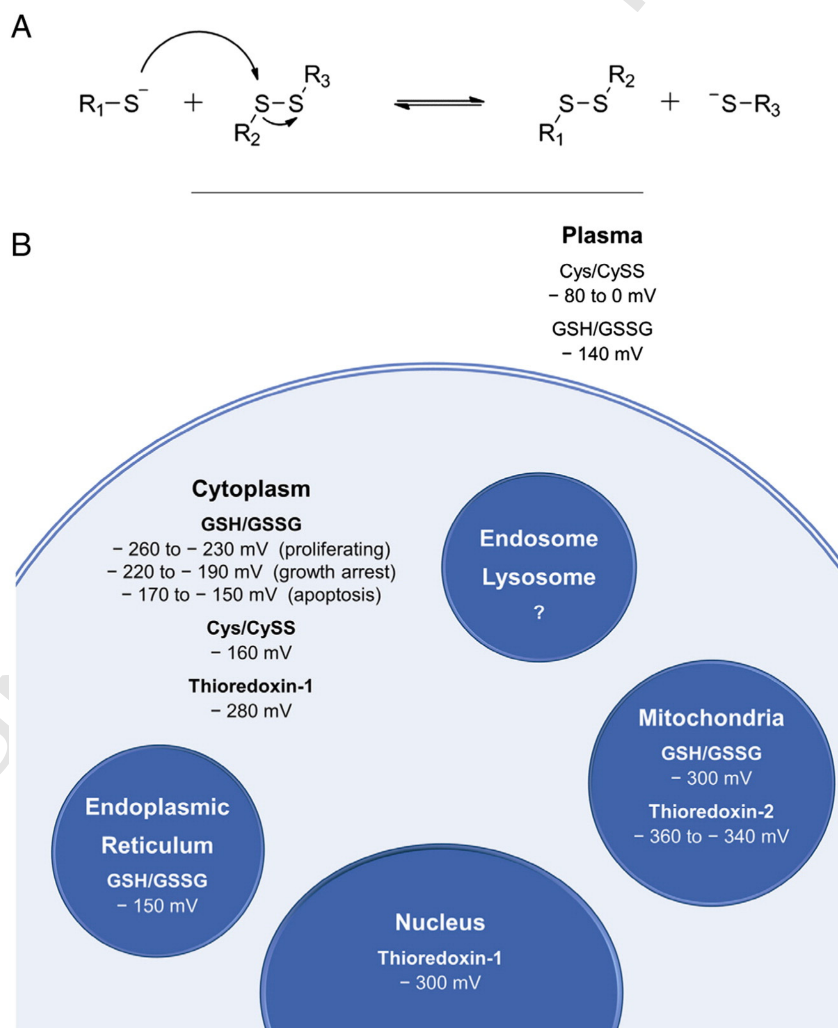

Fig. 1. (A) Disulfide exchange reaction. The equilibrium between thiol and disulfide begins by the nucleophilic attack of a deprotonated thiol (thiolate, RS) on a disulfide bond, resulting in cleavage of this bond while simultaneously producing both a new disulfide and a new thiol. (B) Overview of the steady-state redox potential (E_h) of the most abundant thiol redox couples in different cellular compartments [6,8,9].

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