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Structures and functions of protein disulfide isomerase family members involved in proteostasis in the endoplasmic reticulum

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ABSTRACT

The endoplasmic reticulum (ER) is an essential cellular compartment in which an enormous number of secretory and cell surface membrane proteins are synthesized and subjected to cotranslational or posttranslational modifications, such as glycosylation and disulfide bond formation. Proper maintenance of ER protein homeostasis (sometimes termed proteostasis) is essential to avoid cellular stresses and diseases caused by abnormal proteins. Accumulating knowledge of cysteine-based redox reactions catalyzed by members of the protein disulfide isomerase (PDI) family has revealed that these enzymes play pivotal roles in productive protein folding accompanied by disulfide formation, as well as efficient ER-associated degradation accompanied by disulfide reduction. Each of PDI family members forms a protein–protein interaction with a preferential partner to fulfill a distinct function. Multiple redox pathways that utilize PDIs appear to function synergistically to attain the highest quality and productivity of the ER, even under various stress conditions. This review describes the structures, physiological functions, and cooperative actions of several essential PDIs, and provides important insights into the elaborate proteostatic mechanisms that have evolved in the extremely active and stress-sensitive ER.

Introduction

Protein folding coupled with disulfide bond formation takes place primarily in the endoplasmic reticulum (ER) and contributes to the maturation and stabilization of secretory and cell surface membrane proteins. More than 20 members of the protein disulfide isomerase family (referred to as "PDIs" in this review article) have been identified in the mammalian ER, and some of these enzymes are involved in protein quality control in the early secretory compartment [1,2]. Although PDIs have diverse amino acid sequences and functionalities, they all contain at least one thioredoxin (Trx)-like domain [3–5]. Several factors can regulate the reactivities and substrate specificities of PDIs, including the number, locations, and redox potentials of redox-active Cys–X_{aa}–X_{aa}–Cys motifs and the pK_a values of both the N-terminal and the C-terminal cysteines at the motif. Further, the three-dimensional arrangement of the Trx-like domains and the hydrophobicity or electrostatic potential of the molecular surface can distinguish the functionality of PDIs. Importantly, PDIs most likely work in conjunction with partner proteins, thereby generating specific functions in response to various stresses and demands for the enormous production of secretory proteins, such as immunoglobulins and insulin.

This review summarizes the ways in which PDIs fulfill their distinct functions and work cooperatively to maintain ER quality control. The first part of the review describes the latest insights into the structures and physiological functions of PDIs, focusing on productive protein folding involving disulfide bond formation, and aberrant protein degradation involving disulfide bond reduction. The second part of the review discusses the concerted actions and diverse redox cascades exerted by PDIs and their upstream oxidants/reductants, and raises important issues to reach a comprehensive understanding of the cellular mechanisms underlying the maintenance of protein and redox homeostasis in the mammalian ER.

Structures and functions of PDIs

Structures and functions of PDI and ERp57

Nearly 50 years ago, PDI was identified as an efficient catalyst of disulfide bond formation that is contained abundantly in the

Abbreviations: BiP, binding immunoglobulin protein; CNX, calnexin; CRT, calreticulin; EDEM1, ER-degradation enhancing α-mannosidase-like protein 1; ER, endoplasmic reticulum; ERAD, ER-associated degradation; Ero1, endoplasmic reticulum oxidoreductin 1; GPx, glutathione peroxidase; LDLR, low-density lipoprotein receptor; Prx, peroxiredoxin; QSOX1, quiescin sulfhydryl oxidase 1; Trx, thioredoxin; UPR, unfolded protein response; VKOR, vitamin K epoxide oxidoreductase

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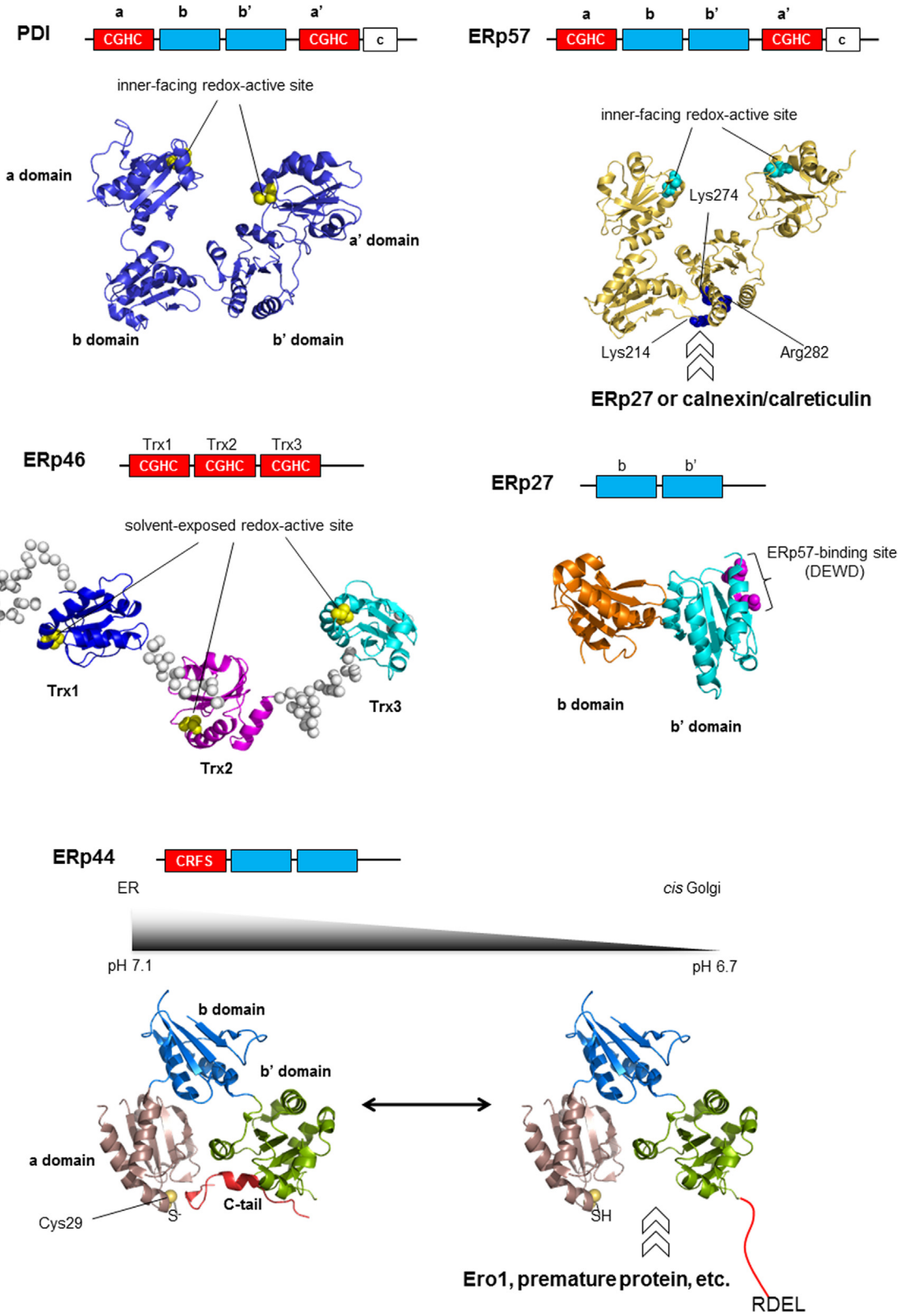

Fig. 1. The domain organizations and overall structures of PDI family members. In the upper panels, the redox-active and redox-inactive Trx-like domains are represented by red and blue boxes, respectively. The sequences of the active sites (Cys–Xaa–Xaa–Cys or Cys–Xaa–Xaa–Ser) are indicated in the red boxes. In the lower panels, the crystal structures of human PDI, ERp57, ERp27, and ERp44, and the solution structure of human ERp46, are represented by ribbon diagrams. The redox-active sites are indicated by yellow spheres. The positively charged region in domain **b**′ of ERp57 and the Asp–Glu–Trp–Asp sequence in domain **b**′ of ERp27 are shown as blue and magenta spheres, respectively. The putative structure of ERp44 with the open C-terminal tail at lower pH values is also shown, and the ER retention signal (Arg–Asp–Glu–Leu: RDEL) is indicated.

microsome fraction [6]. PDI is, though ubiquitous, highly expressed in secretory cells [7]. Canonical PDI comprises four Trx-like domains named **a**, **b**, **b**′, and **a**′ (in order from the N-terminus), which form a compact U-shape with a hydrophobic central cleft (Fig. 1) [8,9]. Domains **a** and **a**′ contain a catalytic Cys–Gly–His–Cys sequence and are redox active; these two active sites face each other across the