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Review

Viral envelope glycoprotein processing by proprotein convertases

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ABSTRACT

The proprotein convertases (PCs) are a family of nine mammalian enzymes that play key roles in the maintenance of cell homeostasis by activating or inactivating proteins *via* limited proteolysis under temporal and spatial control. A wide range of pathogens, including major human pathogenic viruses can hijack cellular PCs for their own purposes. In particular, productive infection with many enveloped viruses critically depends on the processing of their fusion-active viral envelope glycoproteins by cellular PCs. Based on their crucial role in virus-host interaction, PCs can be important determinants for viral pathogenesis and represent promising targets of therapeutic antiviral intervention. In the present review we will cover basic aspects and recent developments of PC-mediated maturation of viral envelope glycoproteins of selected medically important viruses. The molecular mechanisms underlying the recognition of PCs by viral glycoproteins will be described, including recent findings demonstrating differential PC-recognition of viral and cellular substrates. We will further discuss a possible scenario how viruses during co-evolution with their hosts adapted their glycoproteins to modulate the activity of cellular PCs for their own benefit and discuss the consequences for virus-host interaction and pathogenesis. Particular attention will be given to past and current efforts to evaluate cellular PCs as targets for antiviral therapeutic intervention, with emphasis on emerging highly pathogenic viruses for which no efficacious drugs or vaccines are currently available.

Contents

1. Introduction . . . 50
2. PCs are crucial for normal cell function and homeostasis . . . 50
3. Viruses depending on basic aa-specific PCs for glycoprotein processing . . . 51
   3.1. Influenza A virus . . . 51
   3.2. Paramyxoviruses . . . 52
   3.3. Alphaviruses . . . 53
   3.4. Dengue virus . . . 53
   3.5. Human immunodeficiency virus . . . 53
4. Viruses depending on SKI-1/S1P for glycoprotein processing . . . 54
   4.1. Arenaviridae . . . 54
   4.2. Bunyaviridae . . . 55
5. PCs as targets for antiviral therapy . . . 55
   5.1. Basic aa-specific PC inhibitors . . . 55
      5.1.1. Protein-based strategies . . . 55
      5.1.2. Peptide-based compounds and small molecules . . . 56
   5.2. SKI-1/S1P inhibitors . . . 56
      5.2.1. Protein-based strategies . . . 56
      5.2.2. Peptide-based compounds and small molecules . . . 56

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6. Conclusions . . . 56
Acknowledgements . . . 57
References . . . 57

1. Introduction

The proprotein convertases (PCs) are a family of nine mammalian enzymes that play key roles in maintaining cellular and systemic homeostasis by activating or inactivating proteins by limited proteolysis in a spatially and temporally controlled manner. A wide range of pathogens, including major human pathogenic viruses, evolved to hijack cellular PCs and to (ab)use them for their own needs. In particular, productive infection with many enveloped viruses critically depends on the processing of their fusion-active viral envelope glycoproteins by cellular PCs. Based on their crucial role in virus-host interaction, PCs appear as important determinants for the host-range, tissue tropism, and the disease potential of a virus. As essential cellular factors for viral infection they further represent promising targets for antiviral therapeutics.

The present review discusses basic aspects and recent developments in the PC-mediated maturation of viral envelope glycoproteins, in the context of selected viruses of medical importance. We will describe the molecular mechanisms underlying the recognition of PCs by viral glycoproteins and highlight recent findings demonstrating differential recognition of viral and cellular substrates by PCs. In this context, we will propose a possible scenario of how viruses during co-evolution with their hosts have adapted their glycoproteins to modulate the activity of cellular PCs for their own benefit, and discuss the consequences for virus–host interaction and pathogenesis. A last part will cover past and current efforts to evaluate cellular PCs as targets for antiviral drugs, in particular in the context of emerging highly pathogenic viruses for which no efficacious drugs or vaccines are currently available.

2. PCs are crucial for normal cell function and homeostasis

The basic biology of the proprotein convertases (PCs) and their therapeutic potentials have been covered by an excellent recent review (Seidah and Prat, 2012), and only a short summary will be given here. PCs are calcium-dependent serine endoproteases with currently 9 identified family members – PC1/3, PC2, furin, PC4, PACE4, PC5/6, PC7 (basic amino acid (aa)-specific PCs), SKI-1/S1P, and PCSK9 (non basic PCs) (Seidah and Prat, 2002, 2007). They share homology to the yeast kexin subfamily of subtilases with a distinctive "Ser–His–Asp" catalytic triad, which mediates peptide bond scission of substrates that dock into their catalytic pocket (Seidah, 2011).

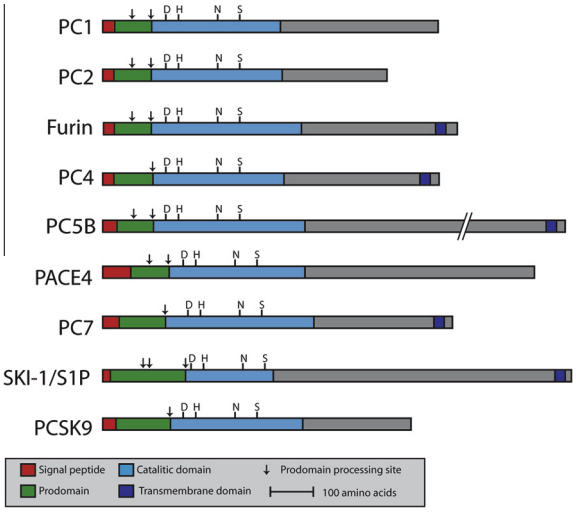

Fig. 1. Schematic representation of the domain arrangement of human proprotein convertases. Residues belonging to the catalytic triad and oxyanion hole are indicated.

All PCs have a well-conserved modular structure comprised of an N-terminal prodomain, followed by a structurally conserved catalytic domain, and variable C-terminal domains (Fig. 1). Four PCs (furin, PC5/6 isoform B, PC7, and SKI-1/S1P) are anchored to cellular membranes while the remaining enzymes are either secreted (PC4, PC5/6 isoform A, PACE4, and PCSK9) or retained in dense core granules (PC1/3, PC2) (Seidah and Prat, 2012) Despite considerable variation in PC sequences, the catalytic subunit cores of these 7 basic aa-specific PCs share $\geqslant$50% sequence identity (Henrich et al., 2005) with similar but not identical recognition of clusters of amino acids (K/RXnK/R↓, *consensus* motif) which interact with the catalytic pocket and define the boundaries of the newly generated fragments. The overall similarity of *consensus* sequences, and thus apparent redundancy of basic aa-specific PCs, suggests overlapping patterns of substrate cleavage, found e.g. in *in vitro* and in overexpression systems. However, there is evidence that subtle differences in amino acid residues in the vicinity of the *consensus* sequence crucial for enzyme/substrate recognition may modulate the preference of a given basic aa-specific PC for specific substrate proteins (Essalmani et al., 2008; Remacle et al., 2006; Zhang et al., 2012). In contrast to basic aa-specific PCs, SKI-1/S1P and PCSK9, the last discovered members of the family, cleave after hydrophobic/small residues, BX(hydrophobic)X↓ (Pasquato et al., 2006) and VFAQ↓, respectively (Benjannet et al., 2004).

A common feature of all PCs is their maturation involving autoproteolytic processing in order to exit the endoplasmic reticulum (ER) and to acquire their specific activity. This step-wise zymogen activation is an essential step in the biosynthesis of basic aa-specific PCs and includes two subsequent cleavages at the N-terminus (Basak et al., 1999; Rousselet et al., 2011). Following removal of the signal peptide in the ER, basic aa-specific PCs auto-process the N-terminal pro-segment, which in turn helps the enzyme polypeptide chain to fold and adopt the correct conformation of the catalytic pocket. The activation of basic aa-specific PCs is regulated in an organelle-specific manner by their pro-segments which undergo pH-dependent auto-cleavage following exit from the ER (Dillon et al., 2012).

The dual function of the pro-segment as chaperone/inhibitor has been well characterized for furin, the prototypic member of PCs. After the first step of prodomain processing, the enzyme is retained in a latent form. The full enzymatic activity is acquired by a second cleavage within the pro-region in a spatially and temporally controlled fashion (Benjannet et al., 2004). Notably, PCs vary in the sub-cellular site of their activation. Furin and PC7 become fully active in the *trans* Golgi network (TGN), PC1/3 and PC2 in the dense core secretory granules, and PC5/6 and PACE4 at the cell surface. In case of SKI-1/S1P (Toure et al., 2000) and differently from basic aa-specific PCs, the two cleavage steps required for activation occur first in the middle of the pro-segment and then at its C-terminus, releasing a fully active enzyme already in the ER/cis Golgi. In contrast to the other PC family members, PCSK9 is kept in a latent form due to the formation of a stable complex with its pro-segment (Piper et al., 2007). With the exception of SKI-1/S1P and PC2, all PC pro-segments are inhibitors of their cognate enzymes (Benjannet et al., 2001; Nour et al., 2003; Zhong et al., 1999).