ARTICLE IN PRESS

Virology ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Virology

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

Retroviral proteases and their roles in virion maturation

Jan Konvalinka[a,b], Hans-Georg Kräusslich[c,d,*], Barbara Müller[c,d]

[a] Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Gilead Sciences and IOCB Research Center, Flemingovo n. 2, 166 10 Prague 6, Czech Republic
[b] Department of Biochemistry, Faculty of Science, Charles University in Prague, Hlavova 8, 128 43 Prague 2, Czech Republic
[c] Department of Infectious Diseases, Virology, University Hospital Heidelberg, Im Neuenheimer Feld 324, 69120 Heidelberg, Germany
[d] Molecular Medicine Partnership Unit, Heidelberg, Germany

ARTICLE INFO

Article history:
Received 19 January 2015
Returned to author for revisions
12 February 2015
Accepted 5 March 2015

Keywords:
Retrovirus
Aspartic protease
Maturation
Human immunodeficiency virus
Gag
Protease inhibitor
Antiretroviral therapy
Resistance
Virus structure

ABSTRACT

Proteolytic processing of viral polyproteins is essential for retrovirus infectivity. Retroviral proteases (PR) become activated during or after assembly of the immature, non-infectious virion. They cleave viral polyproteins at specific sites, inducing major structural rearrangements termed maturation. Maturation converts retroviral enzymes into their functional form, transforms the immature shell into a metastable state primed for early replication events, and enhances viral entry competence. Not only cleavage at all PR recognition sites, but also an ordered sequence of cleavages is crucial. Proteolysis is tightly regulated, but the triggering mechanisms and kinetics and pathway of morphological transitions remain enigmatic.

Here, we outline PR structures and substrate specificities focusing on HIV PR as a therapeutic target. We discuss design and clinical success of HIV PR inhibitors, as well as resistance development towards these drugs. Finally, we summarize data elucidating the role of proteolysis in maturation and highlight unsolved questions regarding retroviral maturation.

© 2015 Elsevier Inc. All rights reserved.

Contents

Introduction: proteases are essential retroviral enzymes . . . 1
Structure and function of retroviral proteases . . . 2
PR as a target for therapeutic intervention . . . 4
  HIV-1 PR as a prime target for antiretroviral chemotherapy . . . 4
  Antiretroviral resistance development . . . 6
  Novel compounds . . . 7
Role of PR in the retroviral replication cycle . . . 7
  Immature and mature retroviral particles: same, but different . . . 7
  Regulation of proteolytic maturation: it is all about control . . . 8
  Role of individual cleavage sites and the functional contribution of spacer peptides . . . 9
  Dynamics and pathway of proteolytic maturation . . . 10
  Role of proteolysis for viral infectivity . . . 11
Conclusion: unsolved mysteries . . . 12
Acknowledgments . . . 12
References . . . 12

Introduction: proteases are essential retroviral enzymes

With genome sizes in the range of 10 kilobases, retroviruses have to rely on strategies of genetic economy in order to encode all proteins required for particle formation, replication and spread.

* Corresponding author at: Department of Infectious Diseases, Virology, University Hospital Heidelberg, Im Neuenheimer Feld 324, 69120 Heidelberg, Germany. Tel.: +49 6221 565001.
E-mail address: hans-georg.kraeusslich@med.uni-heidelberg.de (H.-G. Kräusslich).

http://dx.doi.org/10.1016/j.virol.2015.03.021
0042-6822/© 2015 Elsevier Inc. All rights reserved.

Please cite this article as: Konvalinka, J., et al., Retroviral proteases and their roles in virion maturation. Virology (2015), http://dx.doi.org/10.1016/j.virol.2015.03.021

ARTICLE IN PRESS

A possible way to solve this problem, employed by many different virus groups, is the expression of polyproteins that are subsequently proteolytically processed into functional subunits. Beyond saving space on the genome by using a single set of transcriptional and translational control elements, this approach provides the option to alter the functionality of a particular protein in a controlled manner. Furthermore, it ensures the production of multiple proteins in defined stoichiometry and their targeting to specific sites using a single targeting signal. Retroviruses make use of this strategy by translating their major structural proteins and the viral replication enzymes as part of the group specific antigen (Gag) or polymerase (Pol) polyprotein entity, respectively. Together with the envelope (*env*) open reading frame (ORF), *gag* and *pol* constitute hallmark ORF of all retroviruses (Vogt, 1997).

In a retrovirus-producing cell, viral components assemble into particles in a process mainly orchestrated by the Gag polyprotein, which forms spherical or semi-spherical shells encasing the viral genome. The resulting immature particles are non-infectious, however. Proteolysis of the polyproteins, accompanied by drastic rearrangement of virus architecture, is essential to convert these immature virions into mature, infectious virus (Swanstrom and Wills, 1997). Early biochemical studies on murine and avian retroviruses provided evidence for the synthesis and processing of viral polyproteins (Vogt and Eisenman, 1973; Vogt et al., 1975) and revealed that the corresponding protease is encoded by the virus itself (Dittmar and Moelling, 1978; Vogt et al., 1979; von der Helm, 1977; Yoshinaka and Luftig, 1977). Today, we know that the virus encoded protease (PR) represents an essential enzyme of all retroviruses.

PR itself is encoded as part of a polyprotein whose production often requires a ribosomal frameshift event or read-through of a stop codon. The exact arrangement of the *gag*, *pro* and *pol* ORFs varies between different retroviruses ((Vogt, 1997); Fig. 1). Depending on genome structure, PR is encoded either as part of *gag* (e.g. Rous sarcoma virus (RSV), a member of the avian sarcoma and leucosis viruses, ASLV), as part of *pol* (e.g. human immunodeficiency virus, HIV-1; murine leukemia virus, MLV), or as a separate ORF (e.g. Mason-Pfizer monkey virus, M-PMV). As a consequence, PR is either synthesized in equimolar amounts to Gag, in equimolar amounts to reverse transcriptase (RT) and integrase (IN), or in lower amounts than the structural proteins, but higher than the other enzymes.

Retroviral proteases (correctly denominated“retropepsins“ (Barrett et al., 2012)) and their inhibition have been intensively studied for several decades, and specific aspects are covered in several excellent recent reviews, some of which are cited below. We refer the reader to these reviews for further information and sincerely apologize to all colleagues whose excellent work could not be discussed and cited here due to space limitations.

Structure and function of retroviral proteases

Retropepsins undoubtedly represent the most thoroughly studied proteolytic enzymes in the history of science (Barrett et al., 2012). The last three decades have witnessed an amazing concentration of resources and intellectual potential on the study of these comparatively simple hydrolytic enzymes, leading to an unprecedented accumulation of information regarding their structure, enzymology and inhibition. These efforts have been mostly fueled by the need to develop effective inhibitors of HIV-1 PR as antiviral drugs. Accordingly, HIV-1 PR is by far the most studied of all retropepsins. Other enzymes that have been studied in some detail include the PR of RSV, the prototype alpharetrovirus, of MLV, the prototype gammaretrovirus, and the PRs of HIV-2 and human T-cell leukemia virus (HTLV) due to the pathogenicity of the corresponding viruses. In addition, M-PMV PR has been studied primarily because of its unusual expression (as a separate ORF between *gag* and *pol*) and because of the unique maturation pathway of this betaretrovirus (see below). According to its dominance in the scientific literature, we will focus our review mostly on the description of the structure, substrate specificity and mechanism of action of HIV-1 PR and will discuss specific and divergent features of other retropepsins.

Retropepsins are relatively small aspartic proteases comprised of two identical monomers of 10–15 kDa each (Fig. 2). As other enzymes of this class, they display optimal activity on peptide substrates in vitro under acidic conditions and are poorly active on model peptides at neutral or higher pH (e.g. Billich et al., 1988; Darke et al., 1989; Hyland et al., 1991). Three amino acids in the active site (Asp, Thr/Ser and Gly) form a catalytic triad common to all aspartic proteases. While the cellular aspartic proteases such as pepsin or cathepsin D carry two catalytic aspartates within a single

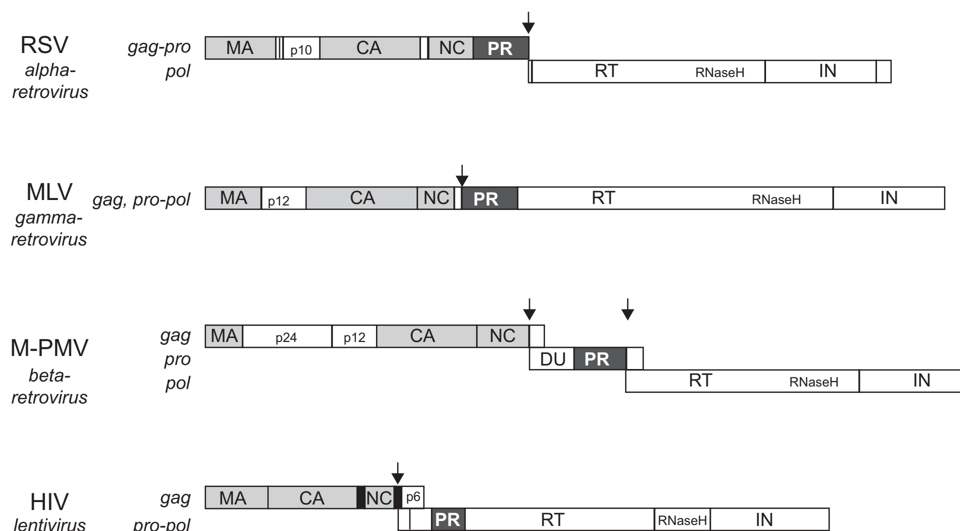

Fig. 1. PR is expressed as part of retroviral polyproteins. The schemes show the genomic localization of the PR encoding region (dark gray box) in different exemplary retroviruses. Vertical lines represent cleavage sites of the respective PR; arrows indicate sites of translational read-through (MLV) or frameshift (other viruses) resulting in expression of Gag–Pro or Gag–Pro–Pol polyproteins, respectively. Canonical Gag domains (MA, CA, NC) are colored light gray. Spacer peptide 1 (SP1) and 2 (SP2) (black boxes) are localized between the CA and NC domains and between the NC and p6 domains of HIV-1 Gag, respectively. RSV, Rous sarcoma virus, MLV, murine leukemia virus; M-PMV, Mason-Pfizer monkey virus; HIV-1, human immunodeficiency virus. DU, dUTPase

Please cite this article as: Konvalinka, J., et al., Retroviral proteases and their roles in virion maturation. Virology (2015), http://dx.doi.org/10.1016/j.virol.2015.03.021

Download English Version:

https://daneshyari.com/en/article/6139209

Download Persian Version:

https://daneshyari.com/article/6139209

Daneshyari.com