Biomedicine & Pharmacotherapy 86 (2017) 221–231

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review

Role of protease and protease inhibitors in cancer pathogenesis and treatment

Ali Eatemadi[a,b,*], Hammed T. Aiyelabegan[a,c], Babak Negahdari[a], Mohammad Ali Mazlomi[a], Hadis Daraee[b,d], Nasim Daraee[b,d], Razieh Eatemadi[e], Esmaeil Sadroddiny[a,*]

[a] Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Medical Biotechnology, School of Medicine, Lorestan University of Medical Sciences, Lorestan, Iran
[c] Tehran University of Medical Sciences International Campus (TUMS-IC), Tehran, Iran
[d] Department of Medical Biotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[e] University of Ilam, Ilam, Iran

ARTICLE INFO

Article history:
Received 25 August 2016
Received in revised form 26 November 2016
Accepted 5 December 2016

Keywords:
Protease
Protease inhibitor
cancer

ABSTRACT

Cancer is the second cause of death in 2015, and it has been estimated to surpass heart diseases as the leading cause of death in the next few years. Several mechanisms are involved in cancer pathogenesis. Studies have indicated that proteases are also implicated in tumor growth and progression which is highly dependent on nutrient and oxygen supply. On the other hand, protease inhibitors could be considered as a potent strategy in cancer therapy. On the basis of the type of the key amino acid in the active site of the protease and the mechanism of peptide bond cleavage, proteases can be classified into six groups: cysteine, serine, threonine, glutamic acid, aspartate proteases, as well as matrix metalloproteases. In this review, we focus on the role of different types of proteases and protease inhibitors in cancer pathogenesis.

Contents

* Corresponding authors at: Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran.
E-mail addresses: a-eatemadi@razi.tums.ac.ir (A. Eatemadi), sadroddiny@sina.tums.ac.ir (E. Sadroddiny).

http://dx.doi.org/10.1016/j.biopha.2016.12.021
0753-3322/

1. Proteases

One of the most important biological catalytic reactions is proteolysis and this is known as proteolytic activity, which has been attributed to a class of enzymes called proteases. Proteolysis is the hydrolysis of peptide bond by attacking the carbonyl group of the peptide. Proteases are of broad enzymes distribution. In human, there are about 990 known protease genes. In addition, about 1605 known protease inhibitor genes have been reported in human [1].

On the basis of the nature of the key amino acid in the active site of the protease and the mechanism of peptide bond cleavage, proteases can be classified into six groups: cysteine, serine, threonine, glutamic acid,aspartate proteases, as well as matrix metalloproteases [2–4].

The cleaving mechanism of a peptide bond with a protease usually occur in the presence of water molecule (in aspartate, metallo- and glutamic acid proteases) or a cysteine, serine, or threonine residue (typically a histidine residue activation) as the nucleophile in the active site [5] (Fig. 1).

The association between stromal and tumor cells modulates two protease systems that are involve in proteolysis outside the cell, these are the MMPs and urokinase plasminogen activator (uPA)/uPA receptor (uPAR)/plasminogen network. Stromal MMP-2 and uPA are synthesized as inactive precursors and then stimulated on the tumor cells surface (Fig. 1), thereby causing malignant cells to rupture the basement membranes. These enzymes also promotes blood vessels sprouting to feed the growing cancer. Antitumor therapies targeting these stromal contributions to metastasis, invasion, and angiogenesis, attack a genetically constant cell population, so they may not attack the resistance related to the use of traditional chemotherapeutic drugs.

2. The role of protease in cancer development

Proteases in normal cells are very essential in carrying out imperative biological processes, and can regulate a diversity of different cellular processes such as gene expression, differentiation, and cell death [6]. However, recent studies have indicated that

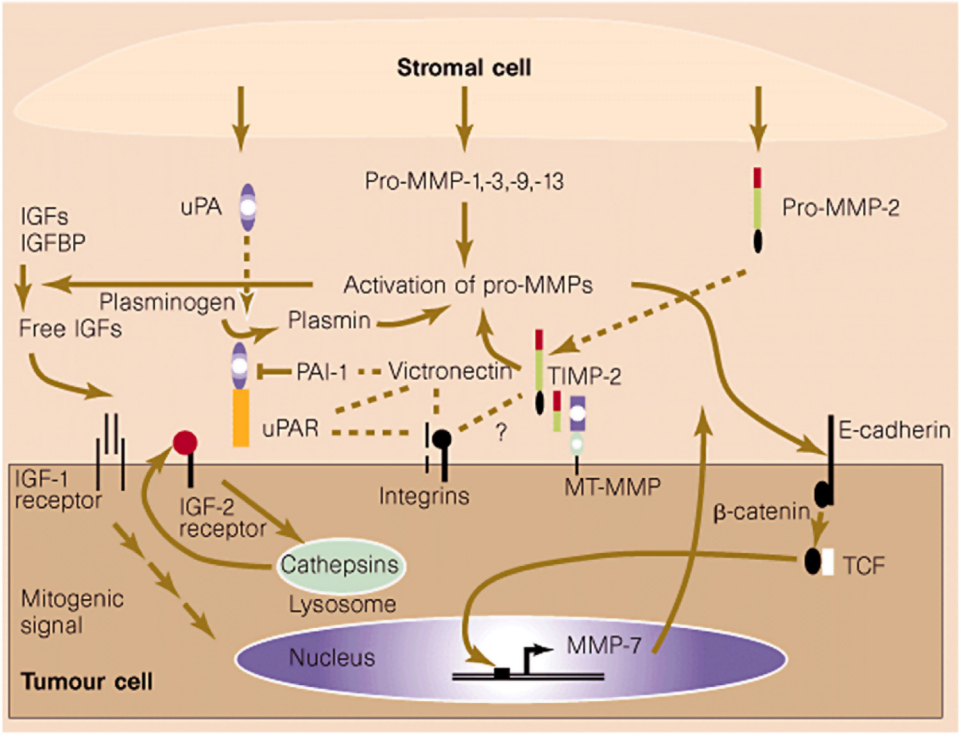

Fig. 1. General cascade of protease inhibitor mechanism of action on tumor cells.

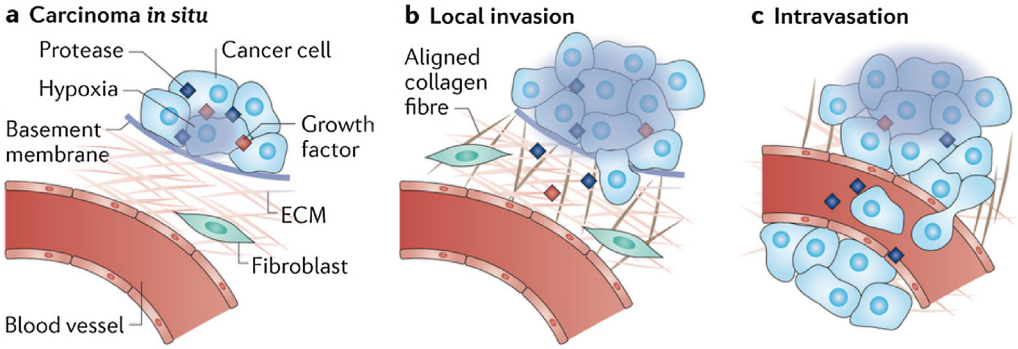

Fig. 2. Epithelial to mesenchymal transition in metastasis.