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Protease-activated receptors as drug targets in inflammation and pain

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ABSTRACT

Proteases have been shown to signal to cells through the activation of a novel class of receptors coupled to G proteins: the protease-activated receptors (PARs). Those receptors are expressed in a wide range of cells, which ultimately are all involved in mechanisms of inflammation and pain. Numerous studies have considered the role of PARs in cells, organ systems or in vivo, highlighting the fact that PAR activation results in signs of inflammation. A growing body of evidences discussed here suggests that these receptors, and the proteases that activate them, interfere with inflammation and pain processes. Whether a role for PARs has been clearly defined in inflammatory and pain pathologies is discussed in this review. Further, the pros and cons for considering PARs as targets for the development of therapeutic options for the treatment of inflammation and pain are discussed.

Contents

1. Introduction

Protease-activated receptors (PARs) have been discovered and cloned in the nineties, when PAR_1 was first identified as the receptor responsible for thrombin-induced aggregation (Rasmussen et al., 1991; Vu et al., 1991). Later on, PAR_2 was cloned (Nystedt et al., 1995; Bohm et al., 1996) and was identified as a receptor sharing the same mechanism of activation as the thrombin receptor PAR_1, but PAR_2 was not activated by thrombin. Instead, PAR_2 was found to be activable by trypsin and mast cell tryptase. Finally, in the late nineties, PAR_3 and PAR_4 were cloned and identified as 2 other thrombin receptors (Ishihara et al., 1997; Xu et al., 1998). Knowledge raised from the human genome cartography suggests that only those 4 receptors share genomic similarities and that no other PARs are to be found in humans. The identification of receptors that are specifically activated by proteases has led the scientific community to consider proteases not merely as degradative enzymes, but truly as signaling molecules that can send specific signals to cells, when those proteases are released and active in cell vicinity. The expression of PARs is ubiquitous among tissues and cell types, and different intracellular signaling pathways have been identified depending on the cell type that is being considered (Macfarlane et al., 2001). Generally, PARs have been

Abbreviations: CGRP, calcitonin gene-related peptide; DSS, dextran sodium sulfate; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IL, interleukin; MMP, matrix metalloprotease; NMDA, N-methyl-D-aspartic acid; PAR, protease-activated receptor; PKA, protein kinase A; PKC, protein kinase C; SP, substance P; Th, T-helper; TNBS, trinitrobenzene sulfonic acid; TNF, tumor necrosis factor; TRPV, transient receptor potential vanilloid; VEGF, vascular endothelial growth factor.

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associated to Gα proteins, but depending on the nature of those proteins (q, 12/13, i, and others), different kinases (protein kinase C, tyrosine kinases, PI3 kinase, RhoGEF, and others) act as second messengers for PAR activation (Macfarlane et al., 2001). Physiological consequences of PAR activation and signaling mechanisms that are activated thus have to be considered independently in each cell type that is being investigated. Concerning the role of PARs in physiology or pathophysiology, they have mostly been studied in the context of pathologies that are associated with a strong protease release. Cancer, vascular diseases and inflammatory conditions (Vergnolle et al., 2001b) constitute major areas of research where efforts have been concentrated to understand the role of PARs. This review will focus on inflammation and chronic pain conditions, trying to consider the pros and cons for developing PAR-based therapies for inflammation and pain-related diseases.

2. Protease-activated receptor cleavage and activation: implications for the pharmacology of the receptors

2.1. Activation

In order for them to be activated, PARs must be cleaved on their extracellular N-terminal domain by proteases. This cleavage releases a

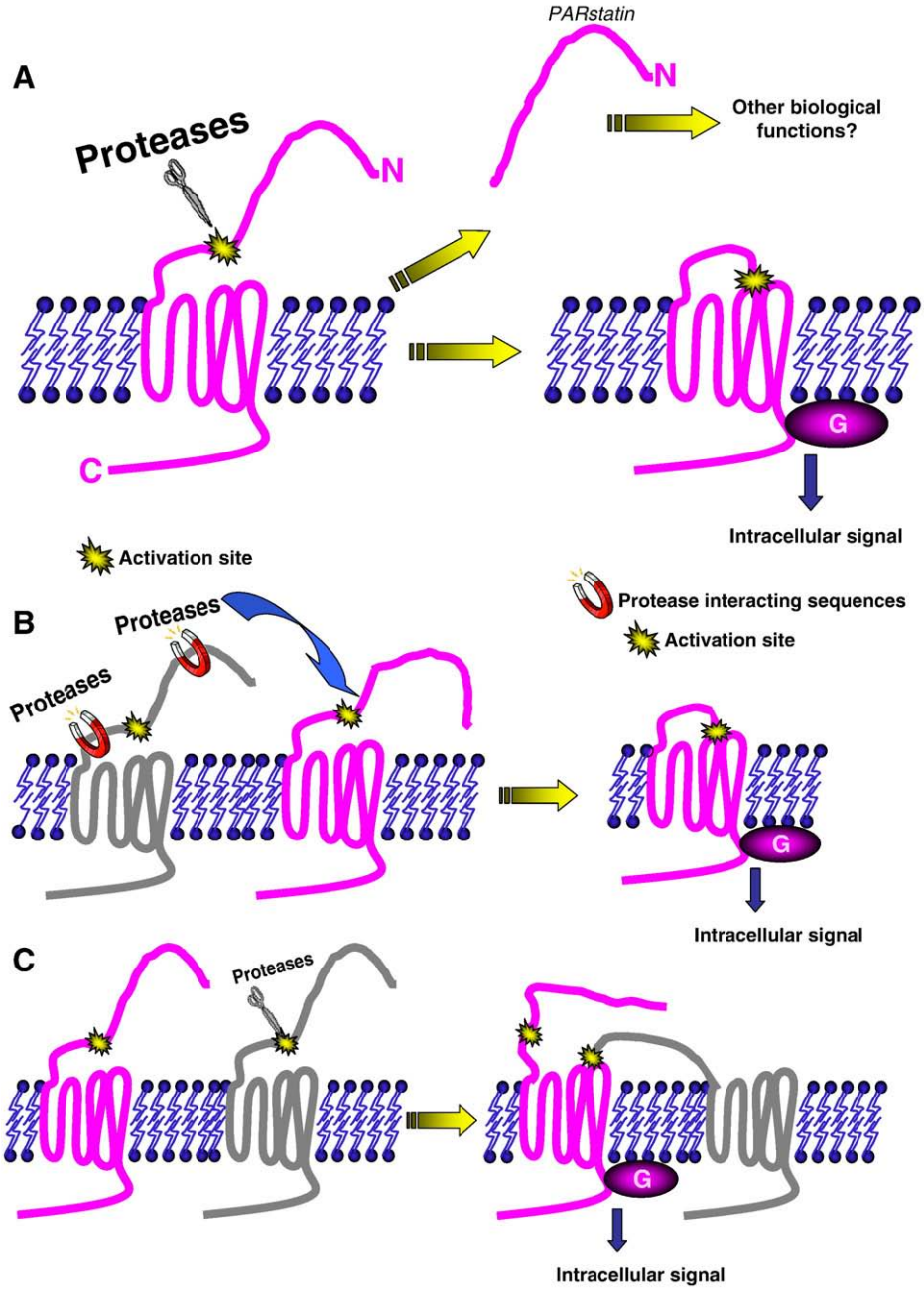

Fig. 1. Mechanisms of activation of PARs. **A**: Proteases cleave at a specific site on the extracellular N-terminal domain and release a new N-terminal domain for the receptor, which acts as a tethered ligand, binding to the second extracellular loop of the receptor to induce intracellular signaling. Specific proteolytic cleavage also releases a small peptide, which is called PARstatin, and which has been shown to exert biological effects, by a mechanism to be discovered. **B**: Some PARs (grey receptor in **B**) have "protease interacting sequences", upstream or downstream from their activation site. These sequences allow the proteases to be attracted to the nearby activation site, facilitating cleavage. Other PARs which do not have "protease interacting sequences" (pink receptor in **B**) can benefit from adjacent "protease interacting sequences" to attract proteases in their vicinity for their activation. **C**: The tethered ligand sequence from a cleaved PAR can trans-activate an adjacent PAR by binding to its second extracellular loop. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)