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A Review on Protease-Activated Receptors

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ABSTRACT

Researchers have also found that "PAR-1 is present in many different types of cells, including immune cells, epithelium, neurons, astrocytes, and fibroblasts. Studies have shown that "it is also present in cancer-associated ECs (epithelial cells), myocytes of blood vessels, mast cells, and macrophages in the area around the tumor". Studies have also concluded that "it stimulates macrophages to synthesize and secrete thrombin and growth factors, which results in increased cell proliferation, tumor growth, and metastasis". In this article, we present a review of role PAR-1.
Key words: *PAR-1, Growth Factor, Epithelial Cell, Thrombin, Tumor Growth.*

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INTRODUCTION

Studies show that mammals have four members of the protease-activated receptor (PAR) family. The genes that make these proteins are called F2R, F2RL1, F2RL3, and F2RL4 [1,2,3,4,5]. In addition to this, in 1991, researchers identified human PAR1 for the very first time as a platelet thrombin receptor [5,6]. Furthermore, studies concluded that PAR2 is unresponsive to thrombin despite the similarity between the human and mouse PAR2 genes and the PAR1 genes [2,7,8]. A lot of research has shown that other thrombin receptors, like PAR3 and PAR4, were discovered because of the strange ways that platelets responded to thrombin in mice that were missing PAR1 [4,9,10]. Researchers have found that the way PAR is controlled is different in different species and tissues. This can be seen in differences in expression levels, protease activity, dimerization with other receptors, compartmentalization, post-translational changes during trafficking, and co-localization with co-receptors.[11]

CLEAVAGE & ACTIVATION

Researchers have found that "exogenous proteases derived from bacteria, plants, fungi, and insects, as well as endogenous proteases, are responsible for the specific cleavage and irreversible activation of PARs".[11] Researchers have also found that "proteases can break certain N-terminal parts of PARs. These enzymes can be soluble or attached to cell membranes (via co-receptors or specialized compartments). As a result, new N-terminal peptides are introduced. These peptides act as ligands then bind to extracellular loop 2 (ECL2)". [5,12]
Researchers have found that because of this interaction, conformational changes are triggered, which in turn change the affinity for intracellular G proteins.[13] Studies have concluded that "there are several different N-terminal cleavage sites, and each of them has a variety of active conformations that have specific G protein preferences".[14] In addition to this, studies have found that "multiple cleavage site-specific cellular responses are often referred to as skewed signaling".[14,15] Researchers have found that, this is the first thing that stops platelets from responding to thrombin.[16] Additionally, studies have found that these truncated PARs are no longer capable of activating themselves through a proteolytic process, but they are still able to do so when exposed to ligands coming from nearby PARs.[17] On the other hand, studies have also found that truncated PARs that behave like the tethered ligand can attach to soluble peptides that are attracted to ECL2 because their structures are similar.[18,19] Several ECL2-binding agonist peptides have been shown to be able to start signaling from both short and long PARs. This has been shown. The characteristics of these peptides have been determined.[11]

PROTEOLYTIC ACTIVATION

Studies have also found that the phase in this "pathway is most likely to slow down the rate of the response. This is because this is the stage that exposes the tethered ligand".[20,21] Studies have also

found that the type of contact that takes place between the enzyme and the substrate is what determines this crucial stage of the process. Proteases can use many different methods, such as cofactors and exosites, to improve the efficiency and selectivity of the hydrolysis of substrates. Studies have further concluded that it has been shown that a diverse range of proteases may activate PARs in a variety of cell types.[22,23,24] Researchers have also found that each protease needs different things to activate PAR, such as cofactors and noncanonical cleavage sites that can set off different signaling pathways. Thrombin is the PAR activator that has received the greatest attention in terms of research and description. Furthermore, studies also concluded that thrombin is a multisubstrate enzyme that utilizes exosites as a means of controlling the substrate specificity of the enzyme as well as the amount of reaction efficiency it generates.[25] Studies have also found that the active site of thrombin is allosterically connected to the exo sites, and that interactions at the exosite-I make thrombin take on the shape of a protease.[26] Studies have also concluded that "it is an excellent substrate because it contains a sequence that looks like hirudin. This sequence interacts with the exosite-I of thrombin, which results in a significant increase in the efficiency of the cleavage".[27,28,29] On the other hand, studiees have also concluded that "structural and biochemical studies have shown that PAR4 does not attach to the exosite-I of the thrombin protein".[30,31,32] Studies have concluded that "enzyme-substrate interaction corresponds to a loss of a factor of 200 in the first-order enzyme constant (kcat) when compared to PAR1, which is 17 s21 as opposed to 340 s21".[29] The fact that PAR4 does not have the advantage of a second binding site. In terms of its underlying mechanism, PAR4 does not benefit from the presence of a second binding site. The results of cleavage studies carried out using pure exodomains provide findings that are consistent with the kinetics of PAR4 activation in the cells.[30,31]
Studies have also found that in vivo proteins are not created in a vacuum, and the complexity of the cell surface has a substantial influence on the PAR activation process. In addition, in vivo proteins are not synthesized in isolation. In addition, researchers found that thrombin is needed for the activation of PAR4 on mouse platelets, which was not what they thought would happen. This was found in the first experiments that were meant to find out what roles PARs play in mutant mice. This requirement was found as a result of the research that was done.[33] In addition, research has shown that Nakanishi-Matsui and colleagues were right when they said that PAR3 is a cofactor that brings thrombin to the surface to help cut the PAR4 substrate.[33] A study also found that "then, Leger et al. discovered a similar strategy for achieving an efficient PAR4 activation rate on human platelets, in which PAR1 acts as a cofactor for PAR4" [33] Studies have also concluded that exosite I is necessary for the rise in PAR4 cleavage that PAR1 causes, and it is crucial for this increase.[30,34] Furthermore, research found that when everything is considered, a reasonable explanation is that the interaction between PAR1 and exosite I not only brings thrombin to the surface of cells, but also keeps it in the shape of a protease so that it can cut PAR4 efficiently.[35] The glycoprotein Ib-IX (GPIb-IX) complex also binds thrombin on platelets. However, it wasn't known what other effects thrombin binding to GPIb had besides creating PAR signaling. This was due to the fact that the GPIb-IX complex also binds thrombin. The glycoprotein Ib-IX (GPIb-IX) complex on platelets is where thrombin binds. [36] Preliminary research suggested that GPIb boosted PAR1 activation by thrombin but had no impact on PAR4 activation at all. This was contrary to the findings of other studies. [37,35] Another study shown that GPIb-IX signaling works in conjunction with PAR signaling via the 14-3-3, Rac1, and LIMK1 axes using cell culture, human platelet rates, and mouse models. [38] According to the findings of these studies, signaling systems may interact with one another downstream of the site of activation without necessarily needing to physically connect with each other.[38]

BIASED SIGNALING

Studies have also found that GPCRs have the ability to transmit signals through both the G protein and b-arrestin pathways. Studies also concluded that agonists that activate specific pathways downstream of the receptor with selectivity are referred to as functional selectivity or biased agonism.Studies on the structure of the b-adrenergic receptor, which is a prototype GPCR, show that distinct changes in the receptor structure coincide with distinct phases of activation using partial agonists.[39,40] Studies also showed that using different agonists makes it clear that only activating a subset of the receptor's molecular switches is needed to start signaling and let the receptor do its job. These intermediate stages provide a structural basis for functional selectivity and allow signaling to proceed along specific pathways. It's possible for posttranslational changes, cofactors, alternative cleavage sites, or drug treatments to cause biased downstream signaling changes, according to many studies.[41,42,43] PAR1 signaling, which is a downstream result of APC and thrombin, may have opposing effects in endothelial cells.[44] In 2011 a study concluded that imbalanced signaling was responsible for this cellular response.[44] According to the source [45], before this study, it was thought that the fact that EPCR and

PAR1 were both found in specific membrane microdomains had a big effect on the APC's cytoprotective signaling that was sent by PAR1. This belief existed prior to the completion of this research.[14,46] On the other hand, researchers had shown that by engaging EPCR with a protein C that is catalytically inactive, it may be possible to change the response of the cell. Based on this previous study, another similar study demonstrated the speed at which APC signals are transmitted through Rac1 in a b-arrestin-2-dependent manner within a five-minute timeframe. In contrast, b-arrestin had no effect on RhoA-mediated thrombin signaling".[15,14,24]

FUTURE DIRECTION [47]
Studies have also shown that "PAR signaling is precisely controlled by the use of different cleavage sites, cofactors, and receptor oligomerization. These mechanisms provide potential novel approaches for therapeutic targeting of PARs. Also, as we learn more about the complex genetic and epigenetic processes that control PAR expression and function, we might be able to target specific groups of people or illnesses based on their genes. Studies have also found that to move these developments forward, it is important to take a broad approach that looks into: (a) the biophysical and structural requirements for PAR activation; (b) the mechanisms that control the start of specific signaling pathways (c) the genetic factors that control the expression and function of PARs or cofactors. Collectively, these factors will ascertain the most logical PARs to target for therapeutic purposes and establish a plan for progress".[47]

CONCLUSION
We come to the conclusion that in-depth molecular research on PAR-1, the progenitor of the PAR family, has led to profound implications for our understanding of cancer's underlying mechanisms. The complex mechanisms of cancer cell proliferation, invasion, and metastasis include PAR-1's active participation. In order to better understand how PAR-1 works as a molecular target for treatment, additional studies on the protein are urgently needed. The significance of PAR-1 agonists in the treatment of clinical cancer is still unknown, despite the fact that they are powerful antiplatelet drugs that are complementary to other antiplatelet medications. It may become a novel target for tumor treatment if it is shown that PAR-1-targeted medicines contribute to tumor growth, invasion, and metastasis rates. It is still early in the development of clinical treatment based on drug research and development that targets the PAR-1 pathway.

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