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Proteinase-activated receptors in GtoPdb v.2023.1

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Abstract

Proteinase-activated receptors (PARs, **nomenclature as agreed by the NC-IUPHAR Subcommittee on Proteinase-activated Receptors [39]**) are unique members of the GPCR superfamily activated by proteolytic cleavage of their amino terminal exodomains. Agonist proteinase-induced hydrolysis unmasks a tethered ligand (TL) at the exposed amino terminus, which acts intramolecularly at the binding site in the body of the receptor to effect transmembrane signalling. TL sequences at human PAR1-4 are SFLLRN-NH_2, SLIGKV-NH_2, TFRGAP-NH_2 and GYPGQV-NH_2, respectively. With the exception of PAR3, synthetic peptides with these sequences (as carboxyl terminal amides) are able to act as agonists at their respective receptors. Several proteinases, including neutrophil elastase, cathepsin G and chymotrypsin can have inhibitory effects at PAR1 and PAR2 such that they cleave the exodomain of the receptor without inducing activation of Gαq-coupled calcium signalling, thereby preventing activation by activating proteinases but not by agonist peptides. Neutrophil elastase (NE) cleavage of PAR1 and PAR2 can however activate MAP kinase signaling by exposing a TL that is different from the one revealed by trypsin [87]. PAR2 activation by NE regulates inflammation and pain responses [115, 76] and triggers mucin secretion from airway epithelial cells [116].

Contents

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References

1. Ahn HS, Foster C, Boykow G, Arik L, Smith-Torhan A, Hesk D and Chatterjee M. (1997) Binding of a thrombin receptor tethered ligand analogue to human platelet thrombin receptor. *Mol Pharmacol* **51**: 350-6 [PMID:9203642]
2. Ahn HS, Foster C, Boykow G, Stamford A, Manna M and Graziano M. (2000) Inhibition of cellular action of thrombin by N3-cyclopropyl-7-[[4-(1-methylethyl)phenyl]methyl]-7H-pyrrolo[3, 2-f]quinazoline-1,3-diamine (SCH 79797), a nonpeptide thrombin receptor antagonist. *Biochem Pharmacol* **60**: 1425-34 [PMID:11020444]
3. Al-Ani B, Saifeddine M, Kawabata A, Renaux B, Mokashi S and Hollenberg MD. (1999) Proteinase-activated receptor 2 (PAR(2)): development of a ligand-binding assay correlating with activation of PAR(2) by PAR(1)- and PAR(2)-derived peptide ligands. *J Pharmacol Exp Ther* **290**: 753-60 [PMID:10411588]
4. Almonte AG, Hamill CE, Chhatwal JP, Wingo TS, Barber JA, Lyuboslavsky PN, David Sweatt J, Ressler KJ, White DA and Traynelis SF. (2007) Learning and memory deficits in mice lacking protease activated receptor-1. *Neurobiol Learn Mem* **88**: 295-304 [PMID:17544303]
5. Almonte AG, Qadri LH, Sultan FA, Watson JA, Mount DJ, Rumbaugh G and Sweatt JD. (2013) Protease-activated receptor-1 modulates hippocampal memory formation and synaptic plasticity. *J Neurochem* **124**: 109-22 [PMID:23113835]
6. Amiable N, Martel-Pelletier J, Lussier B, Kwan Tat S, Pelletier JP and Boileau C. (2011) Proteinase-activated receptor-2 gene disruption limits the effect of osteoarthritis on cartilage in mice: a novel target in joint degradation. *J Rheumatol* **38**: 911-20 [PMID:21285164]
7. Andrade-Gordon P, Maryanoff BE, Derian CK, Zhang HC, Addo MF, Darrow AL, Eckardt AJ, Hoekstra WJ, McComsey DF and Oksenberg D *et al.*. (1999) Design, synthesis, and biological characterization of a peptide-mimetic antagonist for a tethered-ligand receptor. *Proc Natl Acad Sci USA* **96**: 12257-62 [PMID:10535908]
8. Antoniak S, Owens 3rd AP, Baunacke M, Williams JC, Lee RD, Weithäuser A, Sheridan PA, Malz R, Luyendyk JP and Esserman DA *et al.*. (2013) PAR-1 contributes to the innate immune response during viral infection. *J Clin Invest* **123**: 1310-22 [PMID:23391721]
9. Aronovich A, Nur Y, Shezen E, Rosen C, Zlotnikov Klionsky Y, Milman I, Yarimi L, Hagin D, Rechavi G and Martinowitz U *et al.*. (2013) A novel role for factor VIII and thrombin/PAR1 in regulating hematopoiesis and its interplay with the bone structure. *Blood* **122**: 2562-71 [PMID:23982175]
10. Atzori L, Lucattelli M, Scotton CJ, Laurent GJ, Bartalesi B, De Cunto G, Lunghi B, Chambers RC and Lungarella G. (2009) Absence of proteinase-activated receptor-1 signaling in mice confers protection from fMLP-induced goblet cell metaplasia. *Am J Respir Cell Mol Biol* **41**: 680-7 [PMID:19307611]
11. Austin KM, Covic L and Kuliopulos A. (2013) Matrix metalloproteases and PAR1 activation. *Blood* **121**: 431-9 [PMID:23086754]
12. Avet C, Sturino C, Grastilleur S, Gouill CL, Semache M, Gross F, Gendron L, Bennani Y, Mancini JA and Sayegh CE *et al.*. (2020) The PAR2 inhibitor I-287 selectively targets $G\alpha_q$ and $G\alpha_{12/13}$ signaling and has anti-inflammatory effects. *Commun Biol* **3**: 719 [PMID:33247181]
13. Badeanlou L, Furlan-Freguia C, Yang G, Ruf W and Samad F. (2011) Tissue factor-protease-activated

receptor 2 signaling promotes diet-induced obesity and adipose inflammation. *Nat Med* **17**: 1490-7 [PMID:22019885]
14. Barry GD, Suen JY, Le GT, Cotterell A, Reid RC and Fairlie DP. (2010) Novel agonists and antagonists for human protease activated receptor 2. *J Med Chem* **53**: 7428-40 [PMID:20873792]
15. Blackhart BD, Emilsson K, Nguyen D, Teng W, Martelli AJ, Nystedt S, Sundelin J and Scarborough RM. (1996) Ligand cross-reactivity within the protease-activated receptor family. *J Biol Chem* **271**: 16466-71 [PMID:8663335]
16. Boitano S, Hoffman J, Flynn AN, Asiedu MN, Tillu DV, Zhang Z, Sherwood CL, Rivas CM, DeFea KA and Vagner J *et al.*. (2015) The novel PAR2 ligand C391 blocks multiple PAR2 signalling pathways in vitro and in vivo. *Br J Pharmacol* **172**: 4535-4545 [PMID:26140338]
17. Bourgognon JM, Schiavon E, Salah-Uddin H, Skrzypiec AE, Attwood BK, Shah RS, Patel SG, Mucha M, John Challiss RA and Forsythe ID *et al.*. (2013) Regulation of neuronal plasticity and fear by a dynamic change in PAR1-G protein coupling in the amygdala. *Mol Psychiatry* **18**: 1136-45 [PMID:23032873]
18. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
19. Burda JE, Radulovic M, Yoon H and Scarisbrick IA. (2013) Critical role for PAR1 in kallikrein 6-mediated oligodendrogliopathy. *Glia* **61**: 1456-70 [PMID:23832758]
20. Bushell TJ, Cunningham MR, McIntosh KA, Moudio S and Plevin R. (2016) Protease-Activated Receptor 2: Are Common Functions in Glial and Immune Cells Linked to Inflammation-Related CNS Disorders? *Curr Drug Targets* **17**: 1861-1870 [PMID:26648078]
21. Busso N, Frasnelli M, Feifel R, Cenni B, Steinhoff M, Hamilton J and So A. (2007) Evaluation of protease-activated receptor 2 in murine models of arthritis. *Arthritis Rheum* **56**: 101-7 [PMID:17195212]
22. Chackalamannil S, Wang Y, Greenlee WJ, Hu Z, Xia Y, Ahn HS, Boykow G, Hsieh Y, Palamanda J and Agans-Fantuzzi J *et al.*. (2008) Discovery of a novel, orally active himbacine-based thrombin receptor antagonist (SCH 530348) with potent antiplatelet activity. *J Med Chem* **51**: 3061-4 [PMID:18447380]
23. Cheng RKY, Fiez-Vandal C, Schlenker O, Edman K, Aggeler B, Brown DG, Brown GA, Cooke RM, Dumelin CE and Doré AS *et al.*. (2017) Structural insight into allosteric modulation of protease-activated receptor 2. *Nature* **545**: 112-115 [PMID:28445455]
24. Cheng Y, Xi G, Jin H, Keep RF, Feng J and Hua Y. (2014) Thrombin-induced cerebral hemorrhage: role of protease-activated receptor-1. *Transl Stroke Res* **5**: 472-5 [PMID:24323711]
25. Cornelissen I, Palmer D, David T, Wilsbacher L, Concengco C, Conley P, Pandey A and Coughlin SR. (2010) Roles and interactions among protease-activated receptors and P2ry12 in hemostasis and thrombosis. *Proc Natl Acad Sci USA* **107**: 18605-10 [PMID:20930120]
26. Cottrell GS, Amadesi S, Pikios S, Camerer E, Willardsen JA, Murphy BR, Caughey GH, Wolters PJ, Coughlin SR and Peterson A *et al.*. (2007) Protease-activated receptor 2, dipeptidyl peptidase I, and proteases mediate Clostridium difficile toxin A enteritis. *Gastroenterology* **132**: 2422-37 [PMID:17570216]
27. Covic L, Misra M, Badar J, Singh C and Kuliopulos A. (2002) Pepducin-based intervention of thrombin-receptor signaling and systemic platelet activation. *Nat Med* **8**: 1161-5 [PMID:12357249]
28. Crilly A, Palmer H, Nickdel MB, Dunning L, Lockhart JC, Plevin R, McInnes IB and Ferrell WR. (2012) Immunomodulatory role of proteinase-activated receptor-2. *Ann Rheum Dis* **71**: 1559-66 [PMID:22563031]
29. Davidson CE, Asaduzzaman M, Arizmendi NG, Polley D, Wu Y, Gordon JR, Hollenberg MD, Cameron L and Vliagoftis H. (2013) Proteinase-activated receptor-2 activation participates in allergic sensitization to house dust mite allergens in a murine model. *Clin Exp Allergy* **43**: 1274-85 [PMID:24152160]
30. de Boer JD, Van't Veer C, Stroo I, van der Meer AJ, de Vos AF, van der Zee JS, Roelofs JJ and van der Poll T. (2014) Protease-activated receptor-2 deficient mice have reduced house dust mite-evoked allergic lung inflammation. *Innate Immun* **20**: 618-25 [PMID:24048772]
31. De Cunto G, Cardini S, Cirino G, Geppetti P, Lungarella G and Lucattelli M. (2011) Pulmonary hypertension in smoking mice over-expressing protease-activated receptor-2. *Eur Respir J* **37**: 823-34 [PMID:20693251]
32. Edelstein LC, Simon LM, Lindsay CR, Kong X, Teruel-Montoya R, Tourdot BE, Chen ES, Ma L, Coughlin S and Nieman M *et al.*. (2014) Common variants in the human platelet PAR4 thrombin receptor alter platelet function and differ by race. *Blood* **124**: 3450-8 [PMID:25293779]
33. Gardell LR, Ma JN, Seitzberg JG, Knapp AE, Schiffer HH, Tabatabaei A, Davis CN, Owens M, Clemons B

and Wong KK *et al.*. (2008) Identification and characterization of novel small-molecule protease-activated receptor 2 agonists. *J Pharmacol Exp Ther* **327**: 799-808 [PMID:18768780]
34. Georgy SR, Pagel CN, Ghasem-Zadeh A, Zebaze RM, Pike RN, Sims NA and Mackie EJ. (2012) Proteinase-activated receptor-2 is required for normal osteoblast and osteoclast differentiation during skeletal growth and repair. *Bone* **50**: 704-12 [PMID:22173052]
35. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, O'Meara MJ, Rezelj VV, Guo JZ and Swaney DL *et al.*. (2020) A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* **583**: 459-468 [PMID:32353859]
36. Guo H, Liu D, Gelbard H, Cheng T, Insalaco R, Fernández JA, Griffin JH and Zlokovic BV. (2004) Activated protein C prevents neuronal apoptosis via protease activated receptors 1 and 3. *Neuron* **41**: 563-72 [PMID:14980205]
37. Hamill CE, Mannaioni G, Lyuboslavsky P, Sastre AA and Traynelis SF. (2009) Protease-activated receptor 1-dependent neuronal damage involves NMDA receptor function. *Exp Neurol* **217**: 136-46 [PMID:19416668]
38. Hamilton JR, Cornelissen I and Coughlin SR. (2004) Impaired hemostasis and protection against thrombosis in protease-activated receptor 4-deficient mice is due to lack of thrombin signaling in platelets. *J Thromb Haemost* **2**: 1429-35 [PMID:15304051]
39. Hollenberg MD and Compton SJ. (2002) International Union of Pharmacology. XXVIII. Proteinase-activated receptors. *Pharmacol Rev* **54**: 203-17 [PMID:12037136]
40. Hollenberg MD, Renaux B, Hyun E, Houle S, Vergnolle N, Saifeddine M and Ramachandran R. (2008) Derivatized 2-furoyl-LIGRLO-amide, a versatile and selective probe for proteinase-activated receptor 2: binding and visualization. *J Pharmacol Exp Ther* **326**: 453-62 [PMID:18477767]
41. Hollenberg MD, Saifeddine M, al-Ani B and Kawabata A. (1997) Proteinase-activated receptors: structural requirements for activity, receptor cross-reactivity, and receptor selectivity of receptor-activating peptides. *Can J Physiol Pharmacol* **75**: 832-41 [PMID:9315351]
42. Holzhausen M, Spolidorio LC, Ellen RP, Jobin MC, Steinhoff M, Andrade-Gordon P and Vergnolle N. (2006) Protease-activated receptor-2 activation: a major role in the pathogenesis of Porphyromonas gingivalis infection. *Am J Pathol* **168**: 1189-99 [PMID:16565494]
43. Howell DC, Johns RH, Lasky JA, Shan B, Scotton CJ, Laurent GJ and Chambers RC. (2005) Absence of proteinase-activated receptor-1 signaling affords protection from bleomycin-induced lung inflammation and fibrosis. *Am J Pathol* **166**: 1353-65 [PMID:15855637]
44. Jenkins RG, Su X, Su G, Scotton CJ, Camerer E, Laurent GJ, Davis GE, Chambers RC, Matthay MA and Sheppard D. (2006) Ligation of protease-activated receptor 1 enhances alpha(v)beta6 integrin-dependent TGF-beta activation and promotes acute lung injury. *J Clin Invest* **116**: 1606-14 [PMID:16710477]
45. Jiang Y, Yau MK, Lim J, Wu KC, Xu W, Suen JY and Fairlie DP. (2018) A Potent Antagonist of Protease-Activated Receptor 2 That Inhibits Multiple Signaling Functions in Human Cancer Cells. *J Pharmacol Exp Ther* **364**: 246-257 [PMID:29263243]
46. Jimenez-Vargas NN, Pattison LA, Zhao P, Lieu T, Latorre R, Jensen DD, Castro J, Aurelio L, Le GT and Flynn B *et al.*. (2018) Protease-activated receptor-2 in endosomes signals persistent pain of irritable bowel syndrome. *Proc Natl Acad Sci USA* **115**: E7438-E7447 [PMID:30012612]
47. Jin G, Hayashi T, Kawagoe J, Takizawa T, Nagata T, Nagano I, Syoji M and Abe K. (2005) Deficiency of PAR-2 gene increases acute focal ischemic brain injury. *J Cereb Blood Flow Metab* **25**: 302-13 [PMID:15647743]
48. Junge CE, Sugawara T, Mannaioni G, Alagarsamy S, Conn PJ, Brat DJ, Chan PH and Traynelis SF. (2003) The contribution of protease-activated receptor 1 to neuronal damage caused by transient focal cerebral ischemia. *Proc Natl Acad Sci USA* **100**: 13019-24 [PMID:14559973]
49. Kanke T, Ishiwata H, Kabeya M, Saka M, Doi T, Hattori Y, Kawabata A and Plevin R. (2005) Binding of a highly potent protease-activated receptor-2 (PAR2) activating peptide, [3H]2-furoyl-LIGRL-NH2, to human PAR2. *Br J Pharmacol* **145**: 255-63 [PMID:15765104]
50. Kawabata A, Matsunami M, Tsutsumi M, Ishiki T, Fukushima O, Sekiguchi F, Kawao N, Minami T, Kanke T and Saito N. (2006) Suppression of pancreatitis-related allodynia/hyperalgesia by proteinase-activated receptor-2 in mice. *Br J Pharmacol* **148**: 54-60 [PMID:16520745]
51. Kawabata A, Saifeddine M, Al-Ani B, Leblond L and Hollenberg MD. (1999) Evaluation of proteinase-activated receptor-1 (PAR1) agonists and antagonists using a cultured cell receptor desensitization

assay: activation of PAR2 by PAR1-targeted ligands. *J Pharmacol Exp Ther* **288**: 358-70 [PMID:9862790]
52. Kawagoe J, Takizawa T, Matsumoto J, Tamiya M, Meek SE, Smith AJ, Hunter GD, Plevin R, Saito N and Kanke T *et al.*. (2002) Effect of protease-activated receptor-2 deficiency on allergic dermatitis in the mouse ear. *Jpn J Pharmacol* **88**: 77-84 [PMID:11859856]
53. Kennedy AJ, Sundström L, Geschwindner S, Poon EKY, Jiang Y, Chen R, Cooke R, Johnstone S, Madin A and Lim J *et al.*. (2020) Protease-activated receptor-2 ligands reveal orthosteric and allosteric mechanisms of receptor inhibition. *Commun Biol* **3**: 782 [PMID:33335291]
54. Khoufache K, LeBouder F, Morello E, Laurent F, Riffault S, Andrade-Gordon P, Boullier S, Rousset P, Vergnolle N and Riteau B. (2009) Protective role for protease-activated receptor-2 against influenza virus pathogenesis via an IFN-gamma-dependent pathway. *J Immunol* **182**: 7795-802 [PMID:19494303]
55. Knight V, Tchongue J, Lourensz D, Tipping P and Sievert W. (2012) Protease-activated receptor 2 promotes experimental liver fibrosis in mice and activates human hepatic stellate cells. *Hepatology* **55**: 879-87 [PMID:22095855]
56. Kogushi M, Matsuoka T, Kawata T, Kuramochi H, Kawaguchi S, Murakami K, Hiyoshi H, Suzuki S, Kawahara T and Kajiwara A *et al.*. (2011) The novel and orally active thrombin receptor antagonist E5555 (Atopaxar) inhibits arterial thrombosis without affecting bleeding time in guinea pigs. *Eur J Pharmacol* **657**: 131-7 [PMID:21300059]
57. Lam DK and Schmidt BL. (2010) Serine proteases and protease-activated receptor 2-dependent allodynia: a novel cancer pain pathway. *Pain* **149**: 263-72 [PMID:20189717]
58. Lee H, Sturgeon SA, Jackson SP and Hamilton JR. (2012) The contribution of thrombin-induced platelet activation to thrombus growth is diminished under pathological blood shear conditions. *Thromb Haemost* **107**: 328-37 [PMID:22187047]
59. Lee JH, Kim KW, Gee HY, Lee J, Lee KH, Park HS, Kim SH, Kim SW, Kim MN and Kim KE *et al.*. (2011) A synonymous variation in protease-activated receptor-2 is associated with atopy in Korean children. *J Allergy Clin Immunol* **128**: 1326-1334.e3 [PMID:21839502]
60. Lee MC and Huang SC. (2008) Proteinase-activated receptor-1 (PAR(1)) and PAR(2) but not PAR(4) mediate contraction in human and guinea-pig gallbladders. *Neurogastroenterol Motil* **20**: 385-91 [PMID:18179608]
61. LeSarge JC, Thibeault P, Milne M, Ramachandran R and Luyt LG. (2019) High Affinity Fluorescent Probe for Proteinase-Activated Receptor 2 (PAR2). *ACS Med Chem Lett* **10**: 1045-1050 [PMID:31312406]
62. LeSarge JC, Thibeault P, Yu L, Childs MD, Mirka VM, Qi Q, Fox MS, Kovacs MS, Ramachandran R and Luyt LG. (2023) Protease-activated receptor 2 (PAR2)-targeting peptide derivatives for positron emission tomography (PET) imaging. *Eur J Med Chem* **246**: 114989 [PMID:36527934]
63. Lewkowich IP, Day SB, Ledford JR, Zhou P, Dienger K, Wills-Karp M and Page K. (2011) Protease-activated receptor 2 activation of myeloid dendritic cells regulates allergic airway inflammation. *Respir Res* **12**: 122 [PMID:21936897]
64. Li M, Yang X, Zhang Y, Chen L, Lu H, Li X, Yin L and Zhi X. (2015) Activation of protease-activated receptor-2 is associated with increased expression of inflammatory factors in the adipose tissues of obese mice. *Mol Med Rep* **12**: 6227-34 [PMID:26252901]
65. Lindner JR, Kahn ML, Coughlin SR, Sambrano GR, Schauble E, Bernstein D, Foy D, Hafezi-Moghadam A and Ley K. (2000) Delayed onset of inflammation in protease-activated receptor-2-deficient mice. *J Immunol* **165**: 6504-10 [PMID:11086091]
66. Liu S, Liu YP, Yue DM and Liu GJ. (2014) Protease-activated receptor 2 in dorsal root ganglion contributes to peripheral sensitization of bone cancer pain. *Eur J Pain* **18**: 326-37 [PMID:23893658]
67. Liu Y, Ji W, Yin Y, Fan L, Zhang J, Yun H, Wang N, Li Q, Wei Z and Ouyang D *et al.*. (2009) The effects of splicing variant of PXR PAR-2 on CYP3A4 and MDR1 mRNA expressions. *Clin Chim Acta* **403**: 142-4 [PMID:19232333]
68. Luyendyk JP, Mackman N and Sullivan BP. (2011) Role of fibrinogen and protease-activated receptors in acute xenobiotic-induced cholestatic liver injury. *Toxicol Sci* **119**: 233-43 [PMID:20974703]
69. Mao Y, Zhang M, Tuma RF and Kunapuli SP. (2010) Deficiency of PAR4 attenuates cerebral ischemia/reperfusion injury in mice. *J Cereb Blood Flow Metab* **30**: 1044-52 [PMID:20087365]
70. Matej R, Olejar T, Janouskova O and Holada K. (2012) Deletion of protease-activated receptor 2 prolongs survival of scrapie-inoculated mice. *J Gen Virol* **93**: 2057-61 [PMID:22694901]
71. McGuire JJ, Saifeddine M, Triggle CR, Sun K and Hollenberg MD. (2004) 2-furoyl-LIGRLO-amide: a potent and selective proteinase-activated receptor 2 agonist. *J Pharmacol Exp Ther* **309**: 1124-31

[PMID:14976230]
72. McGuire JJ, Van Vliet BN and Halfyard SJ. (2008) Blood pressures, heart rate and locomotor activity during salt loading and angiotensin II infusion in protease-activated receptor 2 (PAR2) knockout mice. *BMC Physiol* **8**: 20 [PMID:18939990]
73. Miller MM, Banville J, Friends TJ, Gagnon M, Hangeland JJ, Lavallée JF, Martel A, O'Grady H, Rémillard R and Ruediger E *et al.*. (2019) Discovery of Potent Protease-Activated Receptor 4 Antagonists with in Vivo Antithrombotic Efficacy. *J Med Chem* **62**: 7400-7416 [PMID:31246024]
74. Moussa L, Apostolopoulos J, Davenport P, Tchongue J and Tipping PG. (2007) Protease-activated receptor-2 augments experimental crescentic glomerulonephritis. *Am J Pathol* **171**: 800-8 [PMID:17640968]
75. Muehlschlegel JD, Perry TE, Liu KY, Fox AA, Smith SA, Lichtner P, Collard CD, Shernan SK, Hartwig JH and Body SC *et al.*. (2012) Polymorphism in the protease-activated receptor-4 gene region associates with platelet activation and perioperative myocardial injury. *Am J Hematol* **87**: 161-6 [PMID:22228373]
76. Muley MM, Reid AR, Botz B, Bölcskei K, Helyes Z and McDougall JJ. (2016) Neutrophil elastase induces inflammation and pain in mouse knee joints via activation of proteinase-activated receptor-2. *Br J Pharmacol* **173**: 766-77 [PMID:26140667]
77. Nagai T, Ito M, Nakamichi N, Mizoguchi H, Kamei H, Fukakusa A, Nabeshima T, Takuma K and Yamada K. (2006) The rewards of nicotine: regulation by tissue plasminogen activator-plasmin system through protease activated receptor-1. *J Neurosci* **26**: 12374-83 [PMID:17122062]
78. Nagai T, Nabeshima T and Yamada K. (2008) Basic and translational research on proteinase-activated receptors: regulation of nicotine reward by the tissue plasminogen activator (tPA) - plasmin system via proteinase-activated receptor 1. *J Pharmacol Sci* **108**: 408-14 [PMID:19098386]
79. Noorbakhsh F, Tsutsui S, Vergnolle N, Boven LA, Shariat N, Vodjgani M, Warren KG, Andrade-Gordon P, Hollenberg MD and Power C. (2006) Proteinase-activated receptor 2 modulates neuroinflammation in experimental autoimmune encephalomyelitis and multiple sclerosis. *J Exp Med* **203**: 425-35 [PMID:16476770]
80. Olejar T, Vetvicka D, Zadinova M, Pouckova P, Kukal J, Jezek P and Matej R. (2014) Dual role of host Par2 in a murine model of spontaneous metastatic B16 melanoma. *Anticancer Res* **34**: 3511-5 [PMID:24982362]
81. Page K, Ledford JR, Zhou P, Dienger K and Wills-Karp M. (2010) Mucosal sensitization to German cockroach involves protease-activated receptor-2. *Respir Res* **11**: 62 [PMID:20497568]
82. Patel YM, Lordkipanidzé M, Lowe GC, Nisar SP, Garner K, Stockley J, Daly ME, Mitchell M, Watson SP and Austin SK *et al.*. (2014) A novel mutation in the P2Y12 receptor and a function-reducing polymorphism in protease-activated receptor 1 in a patient with chronic bleeding. *J Thromb Haemost* **12**: 716-25 [PMID:24612435]
83. Priestley ES, Banville J, Deon D, Dubé L, Gagnon M, Guy J, Lapointe P, Lavallée JF, Martel A and Plamondon S *et al.*. (2022) Discovery of Two Novel Antiplatelet Clinical Candidates (BMS-986120 and BMS-986141) That Antagonize Protease-Activated Receptor 4. *J Med Chem* [PMID:35729784]
84. Rajput PS, Lyden PD, Chen B, Lamb JA, Pereira B, Lamb A, Zhao L, Lei IF and Bai J. (2014) Protease activated receptor-1 mediates cytotoxicity during ischemia using in vivo and in vitro models. *Neuroscience* **281**: 229-40 [PMID:25261684]
85. Ramachandran R, Mihara K, Chung H, Renaux B, Lau CS, Muruve DA, DeFea KA, Bouvier M and Hollenberg MD. (2011) Neutrophil elastase acts as a biased agonist for proteinase-activated receptor-2 (PAR2). *J Biol Chem* **286**: 24638-48 [PMID:21576245]
86. Ramachandran R, Mihara K, Thibeault P, Vanderboor CM, Petri B, Saifeddine M, Bouvier M and Hollenberg MD. (2017) Targeting a Proteinase-Activated Receptor 4 (PAR4) Carboxyl Terminal Motif to Regulate Platelet Function. *Mol Pharmacol* **91**: 287-295 [PMID:28126849]
87. Ramachandran R, Noorbakhsh F, Defea K and Hollenberg MD. (2012) Targeting proteinase-activated receptors: therapeutic potential and challenges. *Nat Rev Drug Discov* **11**: 69-86 [PMID:22212680]
88. Rullier A, Gillibert-Duplantier J, Costet P, Cubel G, Haurie V, Petibois C, Taras D, Dugot-Senant N, Deleris G and Bioulac-Sage P *et al.*. (2008) Protease-activated receptor 1 knockout reduces experimentally induced liver fibrosis. *Am J Physiol Gastrointest Liver Physiol* **294**: G226-35 [PMID:17962354]
89. Sambrano GR, Weiss EJ, Zheng YW, Huang W and Coughlin SR. (2001) Role of thrombin signalling in platelets in haemostasis and thrombosis. *Nature* **413**: 74-8 [PMID:11544528]
90. Schaffner F, Versteeg HH, Schillert A, Yokota N, Petersen LC, Mueller BM and Ruf W. (2010) Cooperation

of tissue factor cytoplasmic domain and PAR2 signaling in breast cancer development. *Blood* **116**: 6106-13 [PMID:20861457]

91. Schouten M, van't Veer C, Roelofs JJ, Levi M and van der Poll T. (2012) Protease-activated receptor-1 impairs host defense in murine pneumococcal pneumonia: a controlled laboratory study. *Crit Care* **16**: R238 [PMID:23270594]
92. Seeliger S, Derian CK, Vergnolle N, Bunnett NW, Nawroth R, Schmelz M, Von Der Weid PY, Buddenkotte J, Sunderkötter C and Metze D *et al.*. (2003) Proinflammatory role of proteinase-activated receptor-2 in humans and mice during cutaneous inflammation in vivo. *FASEB J* **17**: 1871-85 [PMID:14519665]
93. Seitzberg JG, Knapp AE, Lund BW, Mandrup Bertozzi S, Currier EA, Ma JN, Sherbukhin V, Burstein ES and Olsson R. (2008) Discovery of potent and selective small-molecule PAR-2 agonists. *J Med Chem* **51**: 5490-3 [PMID:18720984]
94. Sevastos J, Kennedy SE, Davis DR, Sam M, Peake PW, Charlesworth JA, Mackman N and Erlich JH. (2007) Tissue factor deficiency and PAR-1 deficiency are protective against renal ischemia reperfusion injury. *Blood* **109**: 577-83 [PMID:16990608]
95. Singh VP, Bhagat L, Navina S, Sharif R, Dawra RK and Saluja AK. (2007) Protease-activated receptor-2 protects against pancreatitis by stimulating exocrine secretion. *Gut* **56**: 958-64 [PMID:17114298]
96. Smith SM, Judge HM, Peters G, Armstrong M, Dupont A, Gaussem P and Storey RF. (2005) PAR-1 genotype influences platelet aggregation and procoagulant responses in patients with coronary artery disease prior to and during clopidogrel therapy. *Platelets* **16**: 340-5 [PMID:16194864]
97. Strompfová V, Lauková A and Cilik D. (2013) Synbiotic administration of canine-derived strain Lactobacillus fermentum CCM 7421 and inulin to healthy dogs. *Can J Microbiol* **59**: 347-52 [PMID:23647348]
98. Suen JY, Barry GD, Lohman RJ, Halili MA, Cotterell AJ, Le GT and Fairlie DP. (2012) Modulating human proteinase activated receptor 2 with a novel antagonist (GB88) and agonist (GB110). *Br J Pharmacol* **165**: 1413-23 [PMID:21806599]
99. Takizawa T, Tamiya M, Hara T, Matsumoto J, Saito N, Kanke T, Kawagoe J and Hattori Y. (2005) Abrogation of bronchial eosinophilic inflammation and attenuated eotaxin content in protease-activated receptor 2-deficient mice. *J Pharmacol Sci* **98**: 99-102 [PMID:15879675]
100. Towstyka NY, Shiromizu CM, Keitelman I, Sabbione F, Salamone GV, Geffner JR, Trevani AS and Jancic CC. (2018) Modulation of γδ T-cell activation by neutrophil elastase. *Immunology* **153**: 225-237 [PMID:28888033]
101. Uusitalo-Jarvinen H, Kurokawa T, Mueller BM, Andrade-Gordon P, Friedlander M and Ruf W. (2007) Role of protease activated receptor 1 and 2 signaling in hypoxia-induced angiogenesis. *Arterioscler Thromb Vasc Biol* **27**: 1456-62 [PMID:17363687]
102. Versteeg HH, Schaffner F, Kerver M, Ellies LG, Andrade-Gordon P, Mueller BM and Ruf W. (2008) Protease-activated receptor (PAR) 2, but not PAR1, signaling promotes the development of mammary adenocarcinoma in polyoma middle T mice. *Cancer Res* **68**: 7219-27 [PMID:18757438]
103. Wang J, Jin H, Hua Y, Keep RF and Xi G. (2012) Role of protease-activated receptor-1 in brain injury after experimental global cerebral ischemia. *Stroke* **43**: 2476-82 [PMID:22811450]
104. Wang Y, Zhao Z, Chow N, Ali T, Griffin JH and Zlokovic BV. (2013) Activated protein C analog promotes neurogenesis and improves neurological outcome after focal ischemic stroke in mice via protease activated receptor 1. *Brain Res* **1507**: 97-104 [PMID:23438513]
105. Wee JL, Chionh YT, Ng GZ, Harbour SN, Allison C, Pagel CN, Mackie EJ, Mitchell HM, Ferrero RL and Sutton P. (2010) Protease-activated receptor-1 down-regulates the murine inflammatory and humoral response to Helicobacter pylori. *Gastroenterology* **138**: 573-82 [PMID:19706295]
106. Weiss EJ, Hamilton JR, Lease KE and Coughlin SR. (2002) Protection against thrombosis in mice lacking PAR3. *Blood* **100**: 3240-4 [PMID:12384423]
107. Weithauser A, Bobbert P, Antoniak S, Böhm A, Rauch BH, Klingel K, Savvatis K, Kroemer HK, Tschope C and Stroux A *et al.*. (2013) Protease-activated receptor-2 regulates the innate immune response to viral infection in a coxsackievirus B3-induced myocarditis. *J Am Coll Cardiol* **62**: 1737-45 [PMID:23871888]
108. Wen W, Young SE, Duvernay MT, Schulte ML, Nance KD, Melancon BJ, Engers J, Locuson 2nd CW, Wood MR and Daniels JS *et al.*. (2014) Substituted indoles as selective protease activated receptor 4 (PAR-4) antagonists: Discovery and SAR of ML354. *Bioorg Med Chem Lett* **24**: 4708-13 [PMID:25176330]
109. Wong DM, Tam V, Lam R, Walsh KA, Tatarczuch L, Pagel CN, Reynolds EC, O'Brien-Simpson NM, Mackie EJ and Pike RN. (2010) Protease-activated receptor 2 has pivotal roles in cellular mechanisms involved

in experimental periodontitis. *Infect Immun* **78**: 629-38 [PMID:19933835]

110. Wong PC, Seiffert D, Bird JE, Watson CA, Bostwick JS, Giancarli M, Allegretto N, Hua J, Harden D and Guay J *et al.*. (2017) Blockade of protease-activated receptor-4 (PAR4) provides robust antithrombotic activity with low bleeding. *Sci Transl Med* **9** [PMID:28053157]
111. Xie Q, Xi G, Gong Y, Keep R, Muraszko K and Hua Y. (2013) Protease activated receptor-1 and brain edema formation in glioma models. *Acta Neurochir Suppl* **118**: 191-4 [PMID:23564130]
112. Xue M, Chan YK, Shen K, Dervish S, March L, Sambrook PN and Jackson CJ. (2012) Protease-activated receptor 2, rather than protease-activated receptor 1, contributes to the aggressive properties of synovial fibroblasts in rheumatoid arthritis. *Arthritis Rheum* **64**: 88-98 [PMID:21905006]
113. Yau MK, Suen JY, Xu W, Lim J, Liu L, Adams MN, He Y, Hooper JD, Reid RC and Fairlie DP. (2016) Potent Small Agonists of Protease Activated Receptor 2. *ACS Med Chem Lett* **7**: 105-10 [PMID:26819675]
114. Zhang C, Srinivasan Y, Arlow DH, Fung JJ, Palmer D, Zheng Y, Green HF, Pandey A, Dror RO and Shaw DE *et al.*. (2012) High-resolution crystal structure of human protease-activated receptor 1. *Nature* **492**: 387-92 [PMID:23222541]
115. Zhao P, Lieu T, Barlow N, Sostegni S, Haerteis S, Korbmacher C, Liedtke W, Jimenez-Vargas NN, Vanner SJ and Bunnett NW. (2015) Neutrophil Elastase Activates Protease-activated Receptor-2 (PAR2) and Transient Receptor Potential Vanilloid 4 (TRPV4) to Cause Inflammation and Pain. *J Biol Chem* **290**: 13875-87 [PMID:25878251]
116. Zhou J, Perelman JM, Kolosov VP and Zhou X. (2013) Neutrophil elastase induces MUC5AC secretion via protease-activated receptor 2. *Mol Cell Biochem* **377**: 75-85 [PMID:23392769]
117. Zhou QB, Duan CZ, Jia Q, Liu P and Li LY. (2014) Baicalin attenuates focal cerebral ischemic reperfusion injury by inhibition of protease-activated receptor-1 and apoptosis. *Chin J Integr Med* **20**: 116-22 [PMID:23504578]