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Plasminogen and Its Receptors as Regulators of Cardiovascular Inflammatory Responses

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Abstract

In addition to its role in fibrinolysis, plasminogen (Plg) influences inflammatory cell migration, and thereby plays a prominent role in cardiovascular pathology. The contribution of Plg to inflammatory cell recruitment depends upon its tethering to the surface of responding cells. Plg receptors (Plg-Rs) are heterogeneous and can be classified as tailless, lacking cytoplasmic tails, or tailed, having cytoplasmic tails. *In vivo* observations implicate several tailless Plg-Rs in inflammatory responses. Tailed Plg-Rs on leukocytes include several integrins, which have also been implicated in Plg-dependent responses. Surface expression of both tailless and tailed Plg-Rs can be modulated in number and/or function. A common mechanism involving intracellular calcium mobilization and calcium channels regulates expression of both classes of Plg-Rs. Data are emerging to indicate that targeting Plg and Plg-Rs may limit inflammation and cardiovascular pathology.

Introduction

Inflammation underlies many of the pathological processes leading to cardiovascular diseases. Efficient recruitment of leukocytes from one tissue to another, including from blood, is heavily dependent on proteolysis. Among the various proteases, evidence for involvement of plasmin in inflammation is particularly strong. Numerous studies conducted in Plg-deficient mice have underscored the critical role of Plg in leukocyte recruitment and inflammatory responses (reviewed in (Plow et al. 1999, Plow and Hoover-Plow 2004)). Thus, in addition to its well-established role in fibrinolysis/thrombolysis, Plg is an important mediator of inflammation and hence in cardiovascular diseases.

In this article, we briefly consider how Plg influences inflammatory cell migration. This then leads into a discussion of Plg-R, which we categorize as ones without cytoplasmic tails (*tailless*) and ones with cytoplasmic tails (*tailed*). We then postulate that a common mechanism, changes in intracellular calcium, regulates both classes of Plg-Rs.

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Contributions of Plasminogen to Inflammatory Cell Recruitment

Plg, the zymogen form of the active serine protease, plasmin, circulates at high concentrations in blood (1 μM). Plasmin may contribute to leukocyte migration at several levels. First, plasmin orchestrates degradation of the extracellular matrix (ECM), which serves as a barrier to cell passage. ECM substrates of plasmin include fibronectins, thrombospondins, and laminins as well as fibrin (reviewed in Plow et al. 1995). Additionally, plasmin can activate the matrix metalloproteinases (MMPs) (reviewed in Lijnen, (2000) which degrade collagens. Further influences of Plg on inflammatory cell recruitment stems from its processing of various chemokines/cytokines. Notable in this regard is its processing of transforming growth factor- β , interleukin-1, basic fibroblast growth factor, tumor necrosis factor- α and monocyte chemoattractant protein-1 (reviewed in Ploplis and Castellino, 2000). Plasmin(ogen) also can trigger intracellular signaling events. Plg-mediated signaling occurs in macrophages (Syrovets and Simmet 2004) and neutrophils (Pluskota et al. 2008), and these changes can also influence cell adhesion and migration.

Plasminogen Receptors

Efficient utilization of plasmin(ogen) by cells depends on its tethering to the responding cell. Surface localization enhances Plg activation, increases the catalytic activity of plasmin, and protects the enzyme from inactivation by protease inhibitors, a necessity in an inhibitor-rich environment (reviewed in Plow et al., 1995). The binding of Plg to cell surfaces is mediated by a diverse array of cell surface molecules, collectively Plg-Rs. Common to most Plg-Rs is their ability to interact with the lysine binding sites within the kringle domains of plasmin(ogen). Most of the identified Plg-Rs have a carboxy-terminal lysine, but others harbor internal amino acids that mimic C-terminal lysines. This common recognition mechanism results in similar affinity of Plg for most Plg-Rs ($K_D \sim 1 \mu\text{M}$) (Miles and Plow 1987) and renders these interactions vulnerable to inhibition by basic carboxypeptidases and C-terminal lysine analogs, such as ϵ -aminocaproic acid.

Many Plg-Rs do not contain a signal sequence, transmembrane domain and/or a cytoplasmic tail. Falling into this category of *tailless* Plg-Rs on leukocytes are α -enolase; annexin 2, amphoterin, TIP49a, histone H2B and Plg-R_{KT} (see Table 1). *Tailed* Plg-Rs contain transmembrane and cytoplasmic tails and include several integrin adhesion receptors. Of these, $\alpha\text{V}\beta 3$, $\alpha 5\beta 1$ and $\alpha\text{M}\beta 2$ are present on leukocytes (Table 1). It should be noted that the terminology of *peripheral* versus *integral* membrane proteins could be applied to Plg-Rs with *tailless* corresponding to *peripheral* and *tailed* to *integral* membrane proteins. This designation would change only the classification of Plg-R_{KT}, which is postulated to contain a single intracellular loop with its C-terminal and N-terminal positioned on the exterior of the cell. A hypothetical subcategory of *tailless* Plg-Rs also may arise from the association of Plg binding proteins released from other cells as a consequence of lysis or secretion and then bind to the surface of leukocytes. Indeed, many other Plg binding proteins, such as cytokeratin 8 (Hembrough et al 1995), might function as Plg-Rs through such a mechanism. Both *tailless* and *tailed* Plg-Rs promote Plg activation and pericellular proteolysis, but may display these functions in different biological settings. Regulation of both classes of Plg-Rs by inflammatory stimuli is particularly important in controlling leukocyte responses. Our subsequent discussion focuses on the modulation of Plg-Rs on monocyte cells and neutrophils (PMN) as two cell types pivotal in inflammatory responses associated with cardiovascular diseases.

Tailless Plasminogen Receptors

α -Enolase, first identified as a Plg-R on monocyte cells (Miles et al. 1991), bears a C-terminal lysine, and is now known to function as a Plg-R on many other eukaryotic

(Nakajima et al. 1994, Seweryn et al. 2009, Lopez-Aleman et al. 2003), including transformed cells (Lopez-Aleman et al. 1994) as well as prokaryotic cells (Pancholi and Fischetti 1998). α -Enolase has been directly implicated in macrophage recruitment in LPS-induced lung inflammation in mice and its expression correlates with accumulation of inflammatory cells in the lungs of pneumonia patients (Wygrecka et al. 2009). Annexin 2 (36 kDa), first identified as a Plg-R on endothelial cells, also binds Plg activators (reviewed in Kim and Hajjar, 2002). Annexin 2 is also expressed on monocytoic cells, and its expression is enhanced on acute promyelocytic leukemia cells (Falcone et al. 2001). Annexin 2 does not contain a C-terminal lysine, but may be cleaved to become a Plg-R. However, other studies suggest that annexin 2 only binds Plg when associated with its 11-kDa binding partner, p11, which has lysine as its natural C-terminus (MacLeod et al. 2003).

Histone H2B is present on the surface of leukocytes (Holers and Kotzin 1985), where it functions as a tailless Plg-R (Herren et al. 2006, Das et al. 2007). H2B harbors a C-terminal lysine, as do several other histones (H1, H2A and H2B), which are also likely to function as Plg-Rs if they reach the cell-surface. Several of these histones are detected extracellularly (Brix et al. 1998), some associated with extracellular DNA nets (Brinkmann et al. 2004), and have been implicated in inflammatory responses (Xu et al. 2009). The most recently discovered member among tailless Plg-Rs is Plg-RKT. In contrast to the other tailless Plg-R, Plg-R_{KT} does bear a transmembrane domain, actually two, which are connected by a short cytoplasmic loop. Both its N-terminus and its C-terminus, a lysine, are extracellular (Andronicos et al. 2009).

Blocking studies with antibodies to α -enolase, annexin 2, p11 and H2B indicate that these tailless Plg-Rs account for the preponderance of the Plg binding capacity of monocytoic cells of either murine or human origin (Das et al. 2007) although the effects of antibodies to other Plg-Rs have not been directly compared. Anti-H2B alone blocked ~50% of the Plg binding and Plg activation (Das et al. 2007). Intravenous administration of the anti-H2B Fab fragments inhibited 70% of the Plg-dependent macrophage recruitment in thioglycollate-induced peritoneal inflammation. In this model, Fab fragments of anti-enolase produced modest inhibition in contrast to the marked involvement of α -enolase in lung inflammation induced by LPS (Wygrecka et al. 2009). Also, Plg-R_{KT} cell surface expression was reported to increase upon M-CSF stimulation (Andronicos et al. 2009). Thus, different Plg-Rs may be utilized for inflammatory cell recruitment in a tissue-specific and/or stimulus specific manner.

Cells of the monocytoic lineage change their Plg binding capacity in during a variety of physiological responses, including adhesion (Kim et al. 1996, Herren et al. 2001), apoptosis (O'Mullane and Baker 1999), differentiation (Brownstein et al. 2004, Das et al. 2007, 2009), and agonist stimulation (Herren et al. 2003, Peterson et al. 2003, Wygrecka et al. 2009). In cases where delineated, up-regulation in Plg binding has been accompanied by increases in expression of tailless Plg-Rs: surface expression of H2B, α -enolase, annexin 2 and p11 increased by FACS, Western blots and immunofluorescence when monocytoic cells were differentiated toward macrophages.

Integrins as Tailed plasminogen receptors on leukocytes

Integrins are among the most highly expressed tailed Plg-Rs on leukocytes. The most prominent integrins on leukocytes are the β_2 integrin subfamily. Of these, α M β 2 (Mac-1, CD11b/18), α X β 2, (p150, 95, CD11c/18), and probably α D β 2 (CD11d/18) are Plg-Rs as are α 5 β 1 and α V β 3. Although none of the β_2 integrins contain a C-terminal lysine, they interact with the LBS within Plg kringle domains. Several studies demonstrated that α M β 2 forms a tight complex with uPAR, which enhances integrin-dependent leukocyte

responses (Chapman and Wei 2001). In addition to uPAR, α M β 2 also interacts directly with uPA. Assembly of Plg, uPA, and uPAR on integrin α M β 2 regulates plasmin activity on PMN surface and this tetramolecular complex plays a crucial role in fibrin degradation by PMNs as well as in mediating adhesion and migration of these cells (Pluskota et al. 2003, 2004). As a tailed Plg-R, α M β 2 is capable of directly transmitting “outside-in” signals upon ligand engagement; engagement of α M β 2 by Plg triggers activation of ERK1/2 and Akt (Pluskota et al. 2008). While studies demonstrating the assembly and signaling consequences of Plg binding to α M β 2 have been observed primarily with PMN, it is likely that these mechanisms extend to other α M β 2-bearing cells and to α X β 2 and α D β 2 integrins. Although Plg is abundant in most microenvironments, including blood, these Plg-Rs are not continuously ligated. Plg does not bind unless the integrin is in activated state. Several studies have demonstrated that α V β 3, like α M β 2, recognizes plasmin, uPAR and the kringle domain of uPA, and these interactions influence the adhesive and migratory responses of cells. (Tarui et al. 2006). Of note, not only α M β 2 but also α V β 3 enhances u-PA dependent Plg activation although their role in Plg-dependent cell migration has not been assessed *in vivo*.

Ca²⁺ Mobilization and Channels Provide a Common Pathway for Regulation of Plasminogen Receptors

During monocyte-to-macrophage differentiation, the 3-4-fold up-regulation of the tailless Plg-Rs is independent of new protein synthesis and is unaffected by inhibitors of non-classical protein secretion pathways (ABC-1 transporters, Na/K ATPases, endolysosomal recycling). However, chelation of intracellular Ca²⁺ suppresses differentiation-induced Plg-R expression. Of the various Ca²⁺ channels, only inhibitors of the L-type Ca²⁺ channels (LTCC) prevented Plg-R expression; two different classes of LTCC inhibitors, amlodipine and verapamil prevented up-regulation of Plg-Rs. We detected the Cav1.2 subunit, the pore-forming subunit of the LTCC, in mouse and human macrophages at the transcript and protein levels (Das et al. 2009). Cav1.2 expression increased with differentiation towards macrophages, and knockdown of Cav1.2 with siRNA also blunted Plg-R and Plg binding to the cells. Typically LTCC are voltage gated (VGC). However, expression of LTCC in non-excitatory cells has been reported, where they appear to be gated by agonists, stimulus opened channels (SOC) rather than voltage (Grafton et al. 2003, Stokes et al. 2004).

The LTCC also have been implicated in the regulation of Plg-Rs *in vivo*. Amlodipine or verapamil, administered by implanted minipumps, reduced thioglycolate induced macrophage emigration into the peritoneal cavity by up to 80% at doses that did not effect blood pressure. Macrophages did exit the blood but arrested at the peritoneal membrane, a pattern that was also observed in Plg^{-/-} mice. In addition, the peritoneal tissue in Plg^{-/-} and drug-treated mice became engorged in collagen, an apparent consequence of the absence of Plg-dependent MMP-9 activation (Gong et al. 2008). In the drug-treated mice, the arrested macrophages showed reduced surface expression of H2B, annexin 2 and p11, and showed little surface expression of Plg (Das et al. 2009).

On circulating leukocytes, integrins change their surface expression and functional status, and these alterations are influenced by intracellular Ca²⁺ and Ca²⁺ channels. β 2 integrins are present in subcellular storage vesicles as well as in the plasma membrane. During leukocyte activation, the integrins can rapidly translocate from the storage pools to the cell surface, and “inside-out” signaling events leading to activation of their ligand binding function. A broad range of agonists, including inflammatory mediators, induce Ca²⁺ influx in leukocytes, and antagonists of calcium channels decrease integrin expression and function. For example, ADP/ATP induces Ca²⁺ influx from external stores in monocytes, which results in enhanced ligand binding to integrin α M β 2. These events are blocked by

LTCC antagonists (Altieri et al., 1990). N-propargyl-nitrendipine, a specific blocker of SOC, inhibits α M β 2 cell-surface expression and α M β 2-dependent chemotaxis of PMN. SOC blockade *in vivo* attenuates trauma, hemorrhagic shock-induced PMN priming and lung injury without evidence of hemodynamic side effects in rats (Lee et al. 2005). Mibefradil, an antagonist of T-type Ca²⁺ channels also reduces surface expression of β 2 integrins and L-selectin leading to impaired adhesion of human leukocytes (Nebe et al. 2002). Parallel studies have yet to be conducted to compare the relative effects of these Ca²⁺ blockers on the expression and function of tailed and tailless Plg-Rs, but a dual role of Ca²⁺ mobilization on both classes of Plg-Rs can be anticipated.

Concluding Remarks

In addition to its role as the primary fibrinolytic enzyme, plasmin facilitates cell migration through tissues, including recruitment of inflammatory cells. This function is particularly pertinent to cardiovascular diseases and depends on the binding and activation of Plg to Plg-Rs on the surface of responding cells. Multiple Plg-Rs have been identified, and here we propose a structure-based classification as tailed or tailless Plg-Rs based on the presence or absence of a cytoplasmic domain. Both classes of Plg-Rs have been implicated in the functional responses of leukocytes. Evidence is emerging to suggest that specific classes of Plg-Rs or individual Plg-R contribute to leukocyte responses. Nevertheless, a common mechanism for regulation of Plg-R expression, Ca²⁺ mobilization and Ca²⁺ channels, may be operative. These observations can be synthesized to suggest new anti-inflammatory strategies in which Plg-Rs can be generally targeted with Ca²⁺ channel blockers, even at doses that do not have hemodynamic effects, or can be individually targeted with antagonists of specific Plg-Rs to prevent tissue-specific or stimulus-specific inflammatory responses.

References

- Altieri DC, Wiltse WL, Edgington TS. Signal transduction initiated by extracellular nucleotides regulates the high affinity ligand recognition of the adhesive receptor CD11b/CD18. *J Immunol* 1990;145:662–670. [PubMed: 1973186]
- Andronicos NM, Chen EI, Baik N, et al. Proteomics-based discovery of a novel, structurally unique, and developmentally regulated plasminogen receptor, Plg-RKT, a major regulator of cell surface plasminogen activation. *Blood* 2010;115:1319–1330. [PubMed: 19897580]
- Brinkmann V, Reichard U, Goosmann C, et al. Neutrophil extracellular traps kill bacteria. *Science* 2004;303:1532–1535. [PubMed: 15001782]
- Brix K, Summa W, Lottspeich F, Herzog V. Extracellularly occurring histone H1 mediates the binding of thyroglobulin to the cell surface of mouse macrophages. *J. Clin. Invest* 1998;102:283–293. [PubMed: 9664069]
- Brownstein C, Deora AB, Jacovina AT, et al. Annexin II mediates plasminogen-dependent matrix invasion by human monocytes: enhanced expression by macrophages. *Blood* 2004;103:317–324. [PubMed: 14504107]
- Chapman HA, Wei Y. Protease crosstalk with integrins: the urokinase receptor paradigm. *Thromb Haemost* 2001;86:124–129. [PubMed: 11486997]
- Das R, Burke T, Plow EF. Histone H2B as a functionally important plasminogen receptor on macrophages. *Blood* 2007;110:3763–3772. [PubMed: 17690254]
- Das R, Burke T, Van Wagoner DR, Plow EF. L-type calcium channel blockers exert an antiinflammatory effect by suppressing expression of plasminogen receptors on macrophages. *Circ Res* 2009;105:167–175. [PubMed: 19520970]
- Falcone DJ, Borth W, Khan KMF, Hajjar KA. Plasminogen-mediated matrix invasion and degradation by macrophages is dependent on surface expression of annexin II. *Blood* 2001;97:777–784. [PubMed: 11157497]

- Gong Y, Hart E, Shchurin A, Hoover-Plow J. Inflammatory macrophage migration requires MMP-9 activation by plasminogen in mice. *J Clin Invest* 2008;118:3012–3024. [PubMed: 18677407]
- Grafton G, Stokes L, Toellner KM, Gordon J. A non-voltage-gated calcium channel with L-type characteristics activated by B cell receptor ligation. *Biochem Pharmacol* 2003;66:2001–2009. [PubMed: 14599558]
- Hembrough TA, Vasudevan J, Allietta MM, Glass WF II, Gonias SL. A cytokeratin 8-like protein with plasminogen-binding activity is present on the external surfaces of hepatocytes, HepG2 cells and breast carcinoma cell lines. *J Cell Sci* 1995;108:1071–1082. [PubMed: 7542667]
- Herren T, Burke TA, Das R, Plow EF. Identification of histone H2B as a regulated plasminogen receptor. *Biochemistry* 2006;45:9463–9474. [PubMed: 16878981]
- Herren T, Burke TA, Jardi M, Felez J, Plow EF. Regulation of plasminogen binding to neutrophils. *Blood* 2001;97:1070–1078. [PubMed: 11159539]
- Herren T, Swaisgood CM, Plow EF. Regulation of plasminogen receptors. *Front Biosci* 2003;8:d1–d8. [PubMed: 12456318]
- Holers VM, Kotzin BL. Human peripheral blood monocytes display surface antigens recognized by monoclonal antinuclear antibodies. *J Clin Invest* 1985;76:991–998. [PubMed: 3876357]
- Kim J, Hajjar KA. Annexin II: a plasminogen-plasminogen activator co-receptor. *Front Biosci* 2002;7:d341–d348. [PubMed: 11815288]
- Kim S-O, Plow EF, Miles LA. Regulation of plasminogen receptor expression on monocytoid cells by b1-integrin dependent cellular adherence to extracellular matrix proteins. *J Biol Chem* 1996;271:23761–23767. [PubMed: 8798602]
- Lee C, Xu DZ, Feketeova E, et al. Store-operated calcium channel inhibition attenuates neutrophil function and postshock acute lung injury. *J Trauma* 2005;59:56–63. [PubMed: 16096539]
- Lijnen HR. Molecular interactions between the plasminogen/plasmin and matrix metalloproteinase systems. *Fibrinolysis & Proteolysis* 2000;14:175–181.
- Lopez-Alemanly R, Correc P, Camoin L, Burtin P. Purification of the plasmin receptor from human carcinoma cells and comparison to alpha-enolase. *Thromb Res* 1994;75:371–381. [PubMed: 7997975]
- Lopez-Alemanly R, Suelves M, Munoz-Canoves P. Plasmin generation dependent on alpha-enolase-type plasminogen receptor is required for myogenesis. *Thromb Haemost* 2003;90:724–733. [PubMed: 14515195]
- MacLeod TJ, Kwon M, Filipenko NR, Waisman DM. Phospholipid-associated annexin A2-S100A10 heterotetramer and its subunits: characterization of the interaction with tissue plasminogen activator, plasminogen, and plasmin. *J Biol Chem* 2003;278:25577–25584. [PubMed: 12730231]
- Miles LA, Dahlberg CM, Plescia J, Felez J, et al. Role of cell-surface lysines in plasminogen binding to cells: identification of alpha-enolase as a candidate plasminogen receptor. *Biochemistry* 1991;30:1682–1691. [PubMed: 1847072]
- Miles LA, Plow EF. Receptor mediated binding of the fibrinolytic components, plasminogen and urokinase, to peripheral blood cells. *Thromb Haemost* 1987;58:936–942. [PubMed: 2829380]
- Nakajima K, Hamanoue M, Takemoto N, et al. Plasminogen binds specifically to α -enolase on rat neuronal plasma membrane. *J Neurochem* 1994;63:2048–2057. [PubMed: 7964722]
- Nebe B, Holzhausen C, Rychly J, Urbaszek W. Impaired mechanisms of leukocyte adhesion in vitro by the calcium channel antagonist mibefradil. *Cardiovasc Drugs Ther* 2002;16:183–193. [PubMed: 12374895]
- O'Mullane MJ, Baker MS. Elevated plasminogen receptor expression occurs as a degradative phase event in cellular apoptosis. *Immunol Cell Biol* 1999;77:249–255. [PubMed: 10361257]
- Pancholi V, Fischetti VA. α -enolase, a novel strong plasmin(ogen) binding protein on the surface of pathogenic streptococci. *J Biol Chem* 1998;273:14503–14515. [PubMed: 9603964]
- Peterson EA, Sutherland MR, Nesheim ME, Prydzial EL. Thrombin induces endothelial cell-surface exposure of the plasminogen receptor annexin 2. *J Cell Sci* 2003;116:2399–2408. [PubMed: 12724354]
- Ploplis VA, Castellino FJ. Nonfibrinolytic functions of plasminogen. *Methods* 2000;21:103–110. [PubMed: 10816371]

- Plow EF, Herren T, Redlitz A, Miles LA, Hoover-Plow JL. The cell biology of the plasminogen system. *FASEB J* 1995;9:939–945. [PubMed: 7615163]
- Plow EF, Hoover-Plow J. The functions of plasminogen in cardiovascular disease. *Trends Cardiovasc Med* 2004;14:180–186. [PubMed: 15261889]
- Plow EF, Ploplis VA, Carmeliet P, Collen D. Plasminogen and cell migration in vivo. *Fibrinolysis & Proteolysis* 1999;13:49–53.
- Pluskota E, Soloviev DA, Bdeir K, et al. Integrin $\alpha M\beta 2$ orchestrates and accelerates plasminogen activation and fibrinolysis by neutrophils. *J Biol Chem* 2004;279:18063–18072. [PubMed: 14769799]
- Pluskota E, Soloviev DA, Szpak D, et al. Neutrophil apoptosis: selective regulation by different ligands of integrin $\alpha M\beta 2$. *J Immunol* 2008;181:3609–3619. [PubMed: 18714035]
- Pluskota E, Solovjov DA, Plow EF. Convergence of the adhesive and fibrinolytic systems: recognition of urokinase by integrin $\alpha M\beta 2$ as well as by the urokinase receptor regulates cell adhesion and migration. *Blood* 2003;101:1582–1590. [PubMed: 12393547]
- Seweryn E, Pietkiewicz J, Bednarz-Misa IS, et al. Localization of enolase in the subfractions of a breast cancer cell line. *Z Naturforsch C* 2009;64:754–758. [PubMed: 19957447]
- Stokes L, Gordon J, Grafton G. Non-voltage-gated L-type Ca^{2+} channels in human T cells: pharmacology and molecular characterization of the major α pore-forming and auxiliary β -subunits. *J Biol Chem* 2004;279:19566–19573. [PubMed: 14981074]
- Syrovets T, Simmet T. Novel aspects and new roles for the serine protease plasmin. *Cell Mol. Life Sci* 2004;61:873–885. [PubMed: 15095009]
- Tarui T, Akakura N, Majumdar M, et al. Direct interaction of the kringle domain of urokinase-type plasminogen activator (uPA) and integrin $\alpha v\beta 3$ induces signal transduction and enhances plasminogen activation. *Thromb Haemost* 2006;95:524–534. [PubMed: 16525582]
- Wygrecka M, Marsh LM, Morty RE, et al. Enolase-1 promotes plasminogen-mediated recruitment of monocytes to the acutely inflamed lung. *Blood* 2009;113:5588–5598. [PubMed: 19182206]
- Xu J, Zhang X, Pelayo R, et al. Extracellular histones are major mediators of death in sepsis. *Nat Med* 2009;15:1318–1321. [PubMed: 19855397]

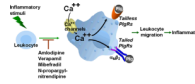


Figure 1.

Role of Ca^{2+} and Ca^{2+} channels in regulation of Plg-Rs. Stimulation of leukocytes, including stimuli that induce differentiation of monocytes into macrophages mobilize Ca^{2+} entry into cells, either through existing channels or by triggering synthesis of Ca^{2+} channels, particularly of the L-type Ca^{2+} channel variety. The pathways involved lead to enhanced expression of both tailed and tailless Plg-Rs at cell surface. Plg binding and activation on leukocytes facilitates leukocyte migration during an inflammatory response. Inhibitors of Ca^{2+} channels can inhibit the upregulation of Plg-Rs and suppress inflammation.

Table 1

Leukocyte Plasminogen Receptors

Tailless Plg-Rs	C-terminal lysine
a-enolase	present
Annexin 2	absent (cleaved to be functional Plg-R)
p11	present
Amphoterin	absent
TIP49a	present
Histone 2B	present
Plg-R _{TK}	present

Tailed Plg-Rs	
α IIb β 3	absent
α v β 3	absent
α 4 β 1	absent
α 5 β 1	absent
α M β 2	absent
gp330	absent