Archives of Oral Biology 74 (2017) 136–145

Contents lists available at ScienceDirect

Archives of Oral Biology

journal homepage: www.elsevier.com/locate/aob

Review

Relevance of the plasminogen system in physiology, pathology, and regeneration of oral tissues – From the perspective of dental specialties

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ARTICLE INFO

Article history:
Received 3 April 2016
Received in revised form 15 September 2016
Accepted 30 September 2016

Keywords:
Plasminogen system
Plasmin
Endodontics
Orthodontics
Periodontics
Oral surgery

ABSTRACT

Plasmin is a proteolytic enzyme that is crucial in fibrinolysis. In oral tissues, the plasminogen system plays an essential role in physiological and pathological processes, which in addition to fibrinolysis include degradation of extracellular matrix, inflammation, immune response, angiogenesis, tissue remodeling, cell migration, and wound healing. Oral tissues reveal a change in the plasminogen system during pathological processes such as periodontitis, peri-implantitis, or pulpitis, as well as in response to mechanical load. The plasminogen system is also a key element in tissue regeneration. The number of studies investigating the plasminogen system in dentistry have grown continuously in recent years, highlighting its increasing relevance in dental medicine. In this review, we present the diverse functions of the plasminogen system in physiology and its importance for dental specialists in pathology and regeneration. We thus provide an overview of the current knowledge on the role of the plasminogen system in the different fields of dentistry, including endodontics, orthodontics, periodontics, and oral surgery.

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http://dx.doi.org/10.1016/j.archoralbio.2016.09.014
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1. Introduction

The role of the plasminogen system in fibrinolysis is well established. In the blood coagulation cascade, the lysis of fibrin clots in the vascular system is crucial in the early phase of tissue wound healing and regeneration (Toriseva and Kähäri, 2009). In the case of blood vessel injuries, the blood coagulation cascade gets activated to stop blood loss (Kisiel and Fujikawa, 1983). In this process, the interaction of several coagulation factors leads to the formation of a blood clot, consisting of a fibrin mesh, to close the wound. The protease plasmin which is activated by the immigrating repair cells allows cleavage of fibrin and the organization in granulation tissue (Brandt, 1985; Heissig et al., 2015).

This step of early wound healing and regeneration is the most studied role of the plasminogen system (Toriseva and Kähäri, 2009). Plasmin is known to be the active form of its proenzyme plasminogen that is converted by the plasminogen activators, urokinase plasminogen activator (uPA) and tissue-type plasminogen activator (tPA) (Castellino and Ploplis, 2005). Besides having different functions, uPA and tPA can be distinguished by differences in molecular weight, affinity for fibrin, and immunoreactivity. For details see Astedt, Wallén, & Aasted, 1979; Rijken, Hoylaerts, & Collen, 1982; Vetterlein & Calton, 1983; Wallén et al., 1983; Wun, Schleuning, & Reich, 1982. Plasminogen is mainly produced in the liver and secreted into the blood circulation where it adopts an activation-resistant conformation (Myöhänen & Vaheri, 2004). The main components of the plasminogen system are (Fig. 1):

uPA: uPA acts in the extracellular space and is primarily involved in cell migration, tissue remodeling, and wound healing. Local concentrations of uPA on the cell surface promote the formation of plasmin and can lead to focused proteolytic activity, which facilitates cell migration and chemotaxis via interaction with high-affinity cell surface receptors (Herbert & Carmeliet, 1998; Manchanda & Schwartz, 1991; Sier et al., 1999). To exert its functions in regulation of proliferation, differentiation, adhesion, and migration, as well as matrix remodeling and inflammation, uPA binds to urokinase plasminogen activator receptors (uPAR) with high specificity (Furlan et al., 2007; von Germar, Barth, & Schwab, 2013).

tPA: The most researched biological function of tPA is fibrinolysis. Having a high affinity for fibrin, it is related to the intravascular breakdown of blood clots by dissolving fibrin in the injured vascular region. tPA is found among other cells in endothelial cells and smooth muscle cells that line the blood vessels (Larsson & Astedt, 1985). Besides fibrinolysis, tPA also contributes to angiogenesis (Díaz, Planaguma, Thomson, Reventós, & Paciucci, 2002) and can enhance cell proliferation (Díaz et al., 2002). Also in the central and peripheral nervous system tPA is found to be relevant in physiological and pathological processes (Kruithof & Dunoyer-Geindre, 2014).

These findings highlight the relevance of the plasminogen activators uPA and tPA for the cell biological mechanisms in physiology, pathology, and regeneration. Their activity is controlled by the plasminogen activator inhibitors. They include plasminogen activator inhibitor type 1 (PAI-1) and type 2 (PAI-2) (Thorsen, Philips, Selmer, Lecander, & Astedt, 1988), protease-nexin I (Baker, Low, Simmer, & Cunningham, 1980), and protein C inhibitor (Geiger et al., 1989), the latter for a while being named PAI-3 (Heeb et al., 1987). Below, we will focus on PAI-1 and PAI-2.

PAI-1: PAI-1 inhibits both uPA and tPA, thus controlling the levels of plasmin generated from plasminogen. It is the

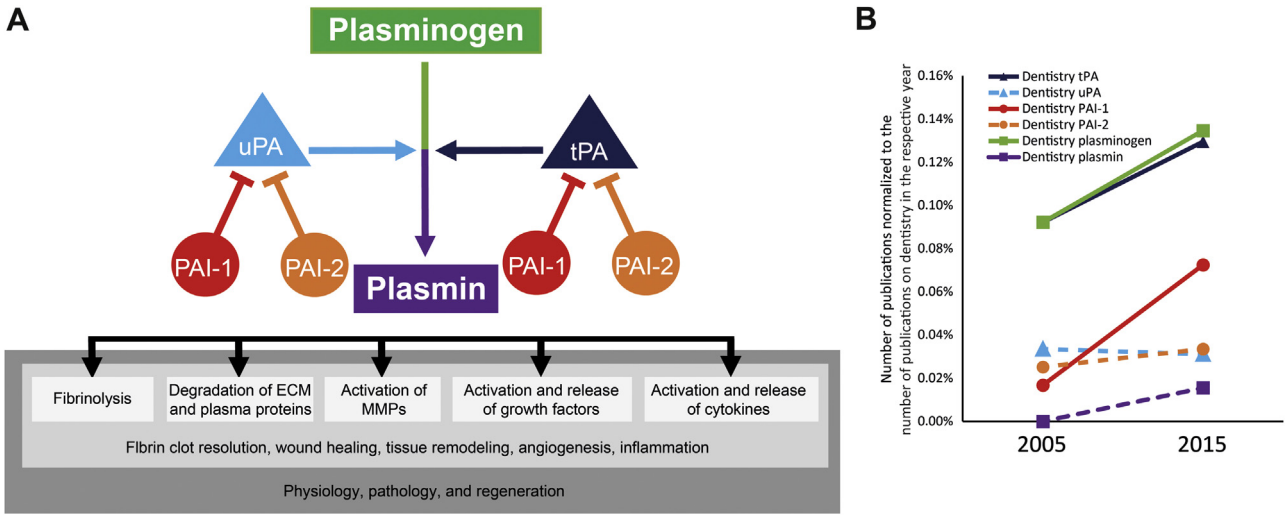

Fig. 1. (A) Schematic representation of the plasminogen system. The transformation of plasminogen into plasmin is catalyzed by urokinase plasminogen activator (uPA) and tissue-type plasminogen activator (tPA). Both activators are controlled by plasminogen activator inhibitor type 1 (PAI-1) and type 2 (PAI-2) (Wyganowska-Swiatkowska et al., 2014). The plasminogen system is involved in fibrinolysis, degradation of extracellular matrix (ECM) and plasma proteins, activation of latent matrix metalloproteinases (MMPs), fibrinolysis, release of cytokines (such as interleukin-1), and activation of growth factors (such as transforming growth factor β (TGFβ), activation and release of fibroblast growth factor (FGF) and insulin-like growth factor-binding protein-4 (IGFBP-4)) (Castellino and Ploplis, 2005). By participating in processes such as fibrin clot resolution, wound healing, tissue remodeling, angiogenesis, and inflammation, the plasminogen activation system is a key player in physiology, pathology, and regeneration of oral tissues (Wyganowska-Swiatkowska et al., 2014). (B) Publication numbers based on a PubMed (http://www.ncbi.nlm.nih.gov) search using the following search strategy: For 'dentistry tPA' with the search terms "(dentistry AND tpa) OR (dentistry AND t-pa) OR (dentistry AND 'tissue plasminogen activator')", for "dentistry uPA" with "(dentistry AND upa) OR (dentistry AND u-pa) OR (dentistry AND 'urokinase plasminogen activator')", for "dentistry PAI-1" with "(dentistry AND pai-1) OR (dentistry AND 'plasminogen activator inhibitor-1')", for "dentistry PAI-2" with "(dentistry AND pai-2) OR (dentistry AND 'plasminogen activator inhibitor-2')", for "dentistry plasminogen" with "dentistry AND plasminogen", and for "dentistry plasmin" with "dentistry AND plasmin" in 2005 ('2005[Date – Publication]') and 2015 ('2015[Date – Publication]'). Publication numbers in the years 2005 and 2015 (Access date: July 7th 2016) are normalized to the number of publications in dentistry in the respective year. Colored symbols represent the respective component of the plasminogen activation system (See also Fig. 1 A).

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