Plasminogen: a pleiotropic inflammatory regulator in radiation-induced wound formation and wound repair

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt förvar i Stora hörsalen (KBE303), KBC-huset, fredagen den 23 november, kl. 09:00.
Avhandlingen kommer att förvaras på engelska.

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Abstract
The plasminogen activator (PA) system plays important roles in many physiological and pathological processes, including inflammation and wound healing. Plasmin, the central component of the PA system, is a broad-spectrum serine protease that is derived from its inactive precursor form, plasminogen. The first aim of this thesis was to study the role of plasminogen in the formation of radiation-induced wounds, which are an inflammatory side effect of radiotherapy. The second aim was to investigate the molecular mechanisms behind the potentiating effect of plasminogen in the healing of radiation-induced wounds. The third aim was to explore the therapeutic potential of plasminogen in the healing of radiation-induced wounds. Radiation therapy in cancer patients is often limited by side effects such as radiation-induced skin damage (radiodermatitis). The mechanisms behind the formation of radiodermatitis are not fully elucidated, and there are no effective preventive therapies for clinical use. In this study, we show that irradiation of skin in WT (wild-type) mice induces plasminogen accumulation, which is followed by activation of TGF-β (transforming growth factor-beta) signaling and the development of inflammation that leads to skin damage. However, plasminogen-deficient mice and mice lacking PAs were mostly resistant to radiodermatitis. Moreover, treatment with a plasminogen inhibitor, tranexamic acid, decreases radiodermatitis in WT mice and prevented radiodermatitis in heterozygous mice. Thus, plasmin is required for the formation of radiodermatitis, and inhibition of plasminogen activation might be a novel treatment strategy to reduce or prevent radiodermatitis in patients undergoing radiotherapy.

Wound healing consists of partially overlapping inflammatory, proliferation, and tissue remodeling phases, and failure to terminate inflammation leads to the formation of chronic wounds. Previous studies by our group have shown that plasminogen is transported to acute wounds by inflammatory cells where it potentiates inflammation and enhances wound healing. Here, we report that plasminogen-deficient mice, which have delayed wound healing, have extensive fibrin and neutrophil depositions in the wounded area long after re-epithelialization, indicating inefficient debridement and chronic inflammation. The delayed formation of granulation tissue suggests that fibroblast function is also impaired in the absence of plasminogen. Therefore, in addition to its role in the activation of inflammation, plasminogen is also crucial for the resolution of inflammation and the activation of the proliferation phase. Importantly, supplementation of plasminogen-deficient mice with human plasminogen leads to a restored healing capacity that is comparable to that in WT mice. Therefore, plasminogen might be an important future therapeutic agent for treatment of wounds. In radiation-induced wounds, inflammation often cannot resolve and the wounds become chronic and fibrotic. Currently, there is no gold standard for the treatment of radiation-induced wounds. In this study, we have shown that radiation-induced wounds treated with plasminogen healed faster than placebo-treated wounds, had diminished inflammation and granulation tissue formation, and had enhanced re-epithelialization and collagen maturation. Transcriptome analysis showed that plasminogen has a pleiotropic effect on gene expression during wound healing, influencing the expression of 33 genes out of the 84 genes studied. In particular, plasminogen decreased the expression of 11 pro-inflammatory genes early in the potentiating gene process. Later, plasminogen decreased WNT (Wingless/Integrated) and TGF-β signaling, as well as the expression of 5 growth factors and 13 factors involved in granulation tissue formation. From the genes downregulated by plasminogen, 19 genes are known to be involved in fibrosis. These results show that in radiation-induced wounds with excessive inflammation and tissue formation plasminogen is able to direct the healing process to a normal outcome without the risk for developing fibrosis. This makes plasminogen an attractive drug candidate for treating radiodermatitis in cancer patients. Taken together, our results indicate that plasminogen is a pleiotropic inflammatory regulator involved in radiation-induced wound formation as well as in wound repair.

Keywords
plasminogen, inflammation, radiodermatitis, wound healing, tranexamic acid