Fibrin is a critical regulator of immunopathology at the oral mucosal barrier

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Fibrin plays an important role in protective physiological processes, such as haemostasis and tissue remodelling, however, due to its proinflammatory properties, excessive fibrin deposits cause chronic inflammation and severe tissue damage via unknown mechanisms. Fibrin removal, fibrinolysis, is achieved by the proteolytic activity of plasmin. The critical role of defective fibrinolysis becomes evident in patients with the autosomal recessive disease: type I plasminogen (Plg) deficiency, which presents with severe immunopathology at barrier surfaces, including the oral mucosa, eye, lung and GI tract. At the oral barrier, Plg-deficient patients present with excessive fibrin deposits and severe periodontitis. In periodontitis, oral mucosal inflammation leads to destruction of tooth-supporting bone and thereby premature loss of teeth. Consistent with observations from plasminogen-deficient patients, mice with severe defects in fibrinolysis (e.g., combined tPA- and uPA-deficiency, Plg-deficiency or plasmin inactivation) displayed spontaneous oral inflammation and severe periodontal bone destruction. Histological characterization of the inflamed periodontal tissue revealed a significant neutrophil/monocyte infiltrate, suggesting a functional link between fibrin accumulation and the recruitment/activation of neutrophils and monocytes. Interestingly, homozygous knock-in Fibγ390-396A mice, which express a mutant form of fibrinogen lacking the β2 myeloid integrin binding site, displayed reduced alveolar bone resorption when compared to the wildtype littermates. Moreover, we were able to rescue this Plg-deficiency-associated periodontal bone destruction by crossing Plg-deficient mice with either fibrin-deficient or Fibγ390-396A mice, suggesting a critical role for the fibrin β2 integrin binding domain in inducing inflammation at the oral barrier. Collectively, our data highlight the role of fibrin as a critical immune-regulator of oral barrier homeostasis and provide opportunities towards understanding the role of fibrin in neutrophil activation and tissue immunity.

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