PROTEASE-ACTIVATED RECEPTOR 2 (PAR2) SIGNALING IN PERIODONTITIS ASSOCIATED WITH TYPE 2 DIABETES

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ABSTRACT:

Background:
Type 2 diabetes (T2D) is one of the major risk factors for the development and progression of periodontitis. Reciprocally, periodontitis may stimulate inflammatory changes in adipose tissue, creating a self-generating cycle, linking obesity, diabetes and periodontal disease. Protease activated receptor 2 (PAR2) is a pro-inflammatory receptor, which plays a role in inflammatory processes. In addition, tissue factor (TF)-PAR2 signaling has been shown to be a major factor in adipose tissue inflammation and insulin resistance. The involvement of PAR2-mediated inflammatory signaling in periodontal disease and how it would play role in the interaction between diabetes and periodontitis is not known.

Aim:
The purpose of this proposal is to investigate the role of PAR2 expression and signaling in periodontal disease associated with T2D and to evaluate the impact of proresolution lipid mediator, Resolvin E1 (RvE1), on PAR2 expression and signaling as a therapeutic approach.

Methods:
Periodontitis will be developed in mice with diabetes (db/db) and transgenic diabetic mice overexpressing the receptor for RvE1 (db/ERV1) and treated with RvE1. Distribution of monocytes and macrophages, PAR2 and TF in the liver and gingival tissue in mice will be evaluated by immunohistochemistry. PAR2 expression in ex vivo culture of mouse macrophages, adipocytes, and signaling regulated by PAR2 in the presence or absence of RvE1 will be further analyzed by FACS, quantitative PCR and Western blotting. Serum, macrophage and adipocyte supernatants will be collected and analyzed by multiplex immunoassay (Luminex) for interleukin (IL)-6, tumor necrosis factor (TNF)-α, and tissue factor (TF). In a parallel clinical study PAR2 and TF expression will be evaluated in banked gingival specimens from patients with T2D (n=10), chronic periodontitis (n=10) and healthy controls (n=10) by immunohistochemistry analysis.

Outcomes:
Molecular mechanisms regulated by PAR2 in periodontitis and T2D will provide basis for new therapeutic approaches. Results of the present study will generate important data on PAR2, a potent pro-inflammatory receptor related to periodontitis, T2D and obesity and the impact of RvE1 on the resolution of inflammation.

SHORT SUMMARY:

Treatment options for periodontitis in susceptible individuals, including those with T2D remain limited, partly due the complex etiology and the challenge of identifying suitable targets which could modulate the inflammatory response. Thus, the investigation of aspects related to inflammation on periodontitis, which can influence such morbidities as T2D and obesity are extremely relevant. In particular, identification of new mechanisms regulated by protease activated receptor 2 (PAR2), with additional benefits of RvE1 treatment, is important considering the results can generate new data regarding the control of inflammation and novel therapeutic approaches with improved outcomes.

AUTHOR STATEMENT:

I am truly honored and humbled to receive the IADR/Philips Oral Healthcare Young Investigator Research Grant. Since my PhD program in periodontics, I have been working with protease activated receptor type 2 (PAR2), an inflammatory receptor, which has shown an important association with periodontal breakdown. This grant will provide a better understanding about the pathogenesis of periodontal disease, the consequence of PAR2 overexpression, its possible correlation with type 2 diabetes and the role of Resolvin E1. In addition to the scientific benefits, developing this project under the guidance of Dr. Kantarci, Dr. Hasturk and Dr. Van Dyke will provide me the great opportunity to learn different concepts and techniques, improving my skills as a periodontal researcher.