Activation of bradykinin B2 Receptors: an Innate Pathway guiding T cell Development in Mice Orally Infected by the Periodontal Bacteria *Porphyromonas gingivalis*.

Julio Scharfstein

Instituto de Biofísica Carlos Chagas Filho (IBCCF)

Our group has recently reported that dendritic cells (DCs), the specialized antigen-presenting cells of the innate immune system, are able to "sense" the presence of kinin-releasing pathogens in host peripheral or lymphoid tissues through the activation of bradykinin B_2 receptors (B_2R). Once activated by kinins, mature DCs migrate to T-cell rich areas of draining lymph nodes, where they present Ag to virgin T cells while at the same time directing development of INF-g-producing T cells. In the present work we verified if these premises are met in the context of oral mucosal infection by *Porphyromonas gingivalis,* a gram-negative bacteria implicated in human periodontitis. Using a mouse infection model based on the inoculation of *P. gingivalis* in the mandibular vestibule (wild type versus $B_2R^{-/-}$ and $TLR2^{-/-}$ mice) we now document that LPS (TLR2 ligand) and gingipain (kinin-releasing cysteine protease) link mucosal inflammation to adaptive immunity. Recall assays performed with fimbria Ag showed that generation of IFN-g-producing T cells and IL-17- producing T cells (exclusively in Balb/C) is critically dependent on the activation of the gingipain®kinin/B_2R signaling pathway at the onset of infection. Analysis of the dynamics of evoked inflammation revealed that TLR2 ligands (eg. LPS) induce plasma leakage via the activation of neutrophils/endothelium, thus allowing for the diffusion of blood-borne kininogens into extravascular tissues. Acting further downstream, gingipain liberates immunostimulatory kinin peptides, i.e., "danger" signals, from kininogens. In short, we demonstrate that LPS and gingipain, respectively acting as TLR2 ligand and kinin-releasing protease, forge a trans-cellular cross-talk between TLR2/B_2R, here characterized as an innate axis that guides fimbriae-specific effector T cell development in mice orally infected by *P. gingivalis*. Additional studies are required to determine if induction of IL-17-producing T cells (an osteoclastogenic T cell subset) via the kinin/B_2R-dependent pathway plays a role in human periodontitis. Supported by CNPq, FAPERJ and Instituto Nacional de Pesquisa em Biologia Estrutural e Bioimagem