803 BACTERIAL BIOFILMS ACTIVATE HUMAN INNATE IMMUNE CELLS

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Systemic Lupus Erythematosus (SLE) is an autoimmune disease with a complex pathogenesis, in which environmental triggers act in individuals with a genetic susceptibility to break immunological self-tolerance. Translational and epidemiological studies indicate that patients with SLE are frequently exposed to microbial products and suggest that bacterial infections may promote SLE in predisposed individuals, *but the underlying mechanisms remain unknown*. We have recently reported that a subset of female patients with SLE, who have asymptomatic persistent bacteriuria, show higher levels of pro-inflammatory markers and disease flares. These patients have high levels of anti-dsDNA antibodies (Abs) that correlate with high levels of Abs against curli/DNA, a bacterial amyloid complexed with bacterial DNA. Curli/DNA is an amyloid produced by Gram-negative bacteria, like UroPathogenic Escherichia coli (UPEC), a frequent cause of bacteriuria and UTI, when they produce biofilms. Bacterial biofilms are structured communities of bacteria that protect bacteria from a hostile environment, including our immune system. We have previously reported that curli/DNA and infections with biofilms accelerate lupus onset in lupus-prone mice and activate immune cells to secrete type I Interferons (IFNs), a cytokine important in lupus pathogenesis. We had also shown that exposure to bacterial biofilms activate murine inflammatory dendritic cells to up-regulate costimulatory molecules and pro-inflammatory cytokines, suggesting an important molecular step in the triggering of lupus flares. We report here that human primary monocytes-derived dendritic cells recognize in vitro bacterial biofilms from E. coli and their best studied PAMP, the amyloid curli/DNA, and activate a pro-inflammatory program. These results establish the human relevance for the investigations of the role of bacterial biofilms in the pathogenesis of SLE.

804 GENETIC DISSECTION OF TLR9 REVEALS COMPLEX REGULATORY AND CRYPTIC PRO-INFLAMMATORY ROLES IN MURINE LUPUS

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In lupus, TLR7 and TLR9 mediate loss of tolerance to RNA and DNA, respectively. Yet, TLR7 promotes while TLR9 protects from disease, implying differences in signaling. To dissect this 'TLR paradox', we generated two TLR9 point mutants—lacking either ligand (TLR9K51E) or MyD88 (TLR9P915H) binding—in lupus-prone MRL/lpr mice. Ameliorated disease of *Tlr9*K51E mice compared to *Tlr9*-/- controls revealed a TLR9 'scaffold' protective function that is ligand- and MyD88-independent. Unexpectedly, *Tlr9*P915H mice were more protected than both *Tlr9*K51E and *Tlr9*WT mice, suggesting that TLR9 also possesses ligand-dependent, but MyD88-independent, regulatory signaling and MyD88-mediated proinflammatory signaling. Triple mixed bone marrow chimeras showed that TLR9-MyD88 independent regulatory roles were B cell-intrinsic and restrained differentiation into pathogenic age-associated B cells (ABC) and plasmablasts (PB). These studies reveal MyD88-independent regulatory roles of TLR9, shedding light on the biology of endosomal TLRs. In addition, we have created TLR7/TLR9 chimeric molecules in the germline of MRL/lpr lupus-prone mice, in which the TIR domains have been switched, and determined the effect on disease outcomes. In this way, we could map the differential regulatory and proinflammatory functions of these two distinct endosomal TLRs.

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Lupus and Cardiovascular Disease

901 CROSS-SECTIONAL ANALYSIS OF LUPUS ERYTHEMATOSUS AND DERMATOMYOSITIS STRESS AND CARDIOVASCULAR HEALTH (LEADS-CV) DATA REVEALS IDEAL CARDIOVASCULAR HEALTH IS RARE IN AFFECTED YOUTH

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Background/Purpose Juvenile lupus (JSLE) and dermatomyositis (JDM) are independent predictors of cardiovascular disease (CVD). The American Heart Association (AHA) defines cardiovascular health (CVH) as the behavioral and biological factors that decrease CVD risk. Prior studies report high rates of hypertension, obesity, and dyslipidemia in JSLE/JDM, but CVH per se has not been assessed in this population.