

with bleomycin that is known to induce fibrotic disease in otherwise normal C57/Bl6 mice, and monitored the animals for disease phenotype.

Methods We injected MRL-MpJ-Fas lpr/lpr (MRL-lpr) mice with bleomycin (100 µg, subcutaneously on upper back) or PBS daily for 14 days. Following which, animals were monitored daily for 14 days. Photographs were taken for skin lesions. On day 28, skin, paws, lung, liver, and kidneys were harvested and tissues sectioned for H and E and Masson Trichrome staining. Immunohistochemistry was performed to detect blood vessels and endothelial cells, namely -smooth muscle actin (SMA) and CD31, respectively. Experiments were repeated in MRL-MpJ-Fas +/+ (MRL+/+) mice.

Results Around day 10 of injections, the tips of front and hind paw digits of 7 of 10 bleomycin-injected MRL-lpr and 3 of 3 bleomycin-injected MRL+/+ mice developed erythematous lesions that ulcerated. None of the controls (5 PBS-injected MRL-lpr, 3 PBS-injected MRL+/+, and 3 bleomycin-injected C57/Bl6 mice) developed such lesions. Such lesions have also not been observed in over 50 unmanipulated MRL-lpr and MRL+/+ mice or over 30 bleomycin-injected C57/Bl6 mice in our animal colony in previous studies. Histological and immunohistochemistry analyses showed increased infiltration, fibrosis, tissue destruction, and CD31 expression in bleomycin-injected MRL-lpr mice as compared to control animals. Masson's trichrome staining revealed significantly increased dermal fibrosis in bleomycin-injected MRL-lpr mice as compared to PBS-injected MRL-lpr mice. Preliminary analysis shows increased alveolar hemorrhage in bleomycin-injected MRL-lpr mice as compared to control mice.

Conclusions The vasculitic lesions that we observed in the digits of bleomycin-injected MRL-lpr and MRL+/+ mice mimics vasculitic lesions seen in patients with lupus. Thus, bleomycin injection in lupus-prone mice can serve as a model for chronic vascular changes seen in lupus and other systemic rheumatic diseases.

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12 EPIGENOME-WIDE ASSOCIATION STUDY REVEALS DIFFERENTIAL DNA METHYLATION IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH A HISTORY OF ISCHEMIC HEART DISEASE

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Background Patients with systemic lupus erythematosus (SLE) have an increased risk of cardiovascular disease (CVD), including ischemic heart disease (IHD). We performed a case-case epigenome-wide association study (EWAS) for IHD in patients with SLE to identify phenotype-specific differences in DNA methylation.

Methods DNA methylation in peripheral blood samples from two independent cohorts of Swedish SLE patients (n=347 and n=201, respectively) was assayed on the HumanMethylation450k BeadChip array, targeting 485,000 CpG sites across the genome. Clinical data were retrieved from medical charts and individuals with a history of CVD were identified in both cohorts. Differential DNA methylation between SLE patients with a history of IHD (n=20 and n=17, respectively) and SLE patients without any CVD events prior to DNA sampling

was tested using a logistic regression model including age, sex and cell type distribution as covariates. Differentially methylated CpG sites in the discovery cohort were defined as $p < 1.3E-7$ for association based on Bonferroni correction and an absolute average difference in methylation beta of $|| > 0.05$. Significance in the replication cohort was determined as $p < 0.05$ and same direction of effect.

Results The top associated differentially methylated CpG sites that were replicated were identified at programmed cell death 1 (PDCD1, $p(\text{disc})=3.2E-13$; $p(\text{repl})=0.03$), perforin 1 (PRF1, $p(\text{disc})=1E-12$; $p(\text{repl})=0.03$) and ZFP36 ring finger protein like 1 (ZFP36L1, $p(\text{disc})=1.3E-11$; $p(\text{repl})=0.002$), all of which are implicated in apoptotic processes. Functional pathway analysis of genes containing sites with altered methylation in SLE IHD pointed to muscle contraction ($p=4.3E-10$), cardiac conduction ($p=2.2E-7$) and role of agrin in postsynaptic differentiation ($p=2.9E-7$) as the most significantly enriched pathways.

Conclusions The results of this study highlight genes and pathways that may be implicated in the pathogenesis of and/or recovery from IHD in patients with SLE. The differentially methylated CpG sites identified in this study can serve as candidates for further evaluation by functional studies and as potential biomarkers for IHD in patients with SLE.

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13 THE ASSOCIATION BETWEEN THE DOSE OF GLUCOCORTICOIDS AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A CROSS-SECTIONAL STUDY

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Background Glucocorticoids (GC) is a mainstay of treatment for systemic lupus erythematosus (SLE) but generally known to affect the health-related quality of life (HRQOL). The aim in this study is to investigate the association between the current dose of GC and HRQOL in SLE patients.

Methods This was a cross-sectional study using baseline data of nationwide SLE patients registry (LUNA) from April 2018 through September 2018. Participants were outpatients with SLE aged 20 years or older. The exposure was the current dose of GC (an equivalent of daily prednisolone). The primary outcome was the HRQOL score of Lupus Patient Reported Outcome (LupusPRO). We included age, sex, and damage in covariates to be particularly considered for the effect of GC-related damage. Damage was divided into GC-related damage and other damage using the SLICC damage index (SDI). GC-related damage was defined as the presence of diabetes mellitus, osteonecrosis, osteoporotic fractures and cataracts. We used a linear regression model to assess the association between the current dose of GC and the HRQOL and further evaluated which of the current daily dose of GC