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Short Communication

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Exposome, Interactome and Systemic Lupus Erythematosus (SLE)-an Evolving Theory and Ongoing Needs

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Abstract

The development and progression of SLE involve complex interactions between genetic, environmental, and immunological factors. Much research is needed to fully elucidate the mechanisms by which these exposures contribute to the development and severity of SLE. Exposome studies, which aim to comprehensively assess an individual's environmental exposures throughout their lifetime, can provide valuable insights into potential risk factors for SLE. By examining the exposome in conjunction with genetic and epigenetic factors, researchers can identify associations between specific exposures and the development or severity of the disease. This approach can help uncover modifiable risk factors and guide the development of preventive strategies for SLE, regardless of an individual's genetic background. Furthermore, an "interactome" approach, which investigates the complex network of interactions between genes, proteins, and environmental factors, can be instrumental in understanding SLE at a systems level. By integrating data from the exposome, genome, and epigenome, researchers can gain a more comprehensive understanding of the disease's etiology, identify populations at risk, and potentially develop personalized prognostication and therapeutic approaches.

Introduction

Several environmental exposures have been suggested to be associated with the development of SLE. Current smoking, exposure to crystalline silica and intake of exogenous hormones comprise the strongest increase in relative risk by a factor 1.5, 2.1–4.6 and 1.5–1.9, respectively [1]. Pesticides, chemical and industrial exposures have been suggested to increase risk of SLE by a factor of 1.5-7.4 in various settings [2]. Metabolomic studies have demonstrated a close association between welding fume exposure and systemic inflammation It has also been speculated that several infectious agents may trigger the development of SLE and increase the severity of the clinical phenotype; although EBV-associated infectious mononucleosis was not associated with SLE in a registry-based population study [3].Other evidence suggest a lack of control of Epstein-Barr virus (EBV) infection in SLE patients.The development and progression of SLE involve complex interactions between genetic, environmental, and immunological factors. Further research is needed to fully elucidate the mechanisms by which these exposures contribute to the development and severity of SLE

Gene Protein Exposure Interaction - Interactome

Exposome studies, which aim to comprehensively assess an individual's environmental exposures throughout their lifetime, can provide valuable insights into potential risk factors for SLE. By examining the exposome in conjunction with genetic and epigenetic factors, researchers can identify associations between specific exposures and the development or severity of the disease. This approach can help uncover modifiable risk factors and guide the development of preventive strategies for SLE, regardless of an individual's genetic background. Furthermore, an "interactome" approach, which investigates the complex network of interactions between genes, proteins, and environmental factors, can be instrumental in understanding SLE at a systems level. By integrating data from the exposome, genome, and epigenome, researchers can gain a more comprehensive understanding of the disease's etiology, identify populations at risk, and potentially develop personalized prognostication and therapeutic approaches.

The cross-field between the genome and the exposome is enormous but of even greater interest as it has still not been possible to single out any environmental or genetic factors that come just near defining a comprehensive risk model of SLE. However, environmental factors may interact with genetics by several mechanisms, which may have the potential to add significantly to such wanted risk models. Epigenetics are stable and heritable, yet reversible,

mechanisms that regulate gene expression without altering the underlying gene code. Aberrant DNA methylation patterns have been increasingly recognized in SLE patients compared to healthy controls in epigenome-wide association studies (EWAS) [4]. These have consistently suggested a pattern of DNA hypomethylation of IFN-regulated genes, such as IFI44L, PARP9, IFITM1 and MX1, in CD4+ T cells, monocytes, granulocytes and B cells as well as in white blood cells (WBCs) in general.Differential methylation of WBCs in SLE patients has even been suggested to be associated with the presence of SLE-related autoantibodies. A study showed that hypomethylation of interferon-regulated genes occurs in all major cellular compartments in SLE-affected twins [5].

Studies on Genome-Exposome (G-E) Exposure in Lupus

Fraser et al studied occupational sunlight exposure based on job history obtained for each job lasting 12 or more months, and based on a question asking if the job involved work in the sun for 10 or more hours per week for at least 3 months of the year; months in these jobs was summed up to the diagnosis age for cases or corresponding reference age for controls. In the combined analysis of occupational sunlight exposure and GSTM1 genotype, the effect of sun exposure among Caucasians varied depending on GSTM1 genotype. There was a 3-fold increased risk (OR 3.1, 95% CI 0.9, 10.8) of SLE associated with 24 or more months' occupational sun exposure among Caucasians with the GSTM1 null genotype, but sun exposure was not associated with risk among GSTM1 positive Caucasians (OR 0.6, 95% CI 0.3, 1.5) [6]. The interaction was statistically significant (p = 0.028) for Caucasians but not for African Americans.

Occupational exposure to sunlight was somewhat associated with the presence of anti-Ro antibodies among cases, but the difference was not statistically significant (age, sex, and race adjusted OR 1.9, 95% CI 0.9, 4.0 for ≥ 24 mo compared with < 24 mo occupational sunlight exposure). This association was similar in Caucasians (OR 2.2, 95% CI 0.6,7.6) and African-Americans (OR 1.6, 95% CI 0.6, 4.3).

A gene-environment interaction was suggested by Kiyohara C et al in their study. Combination of the TNFRSF1B rs1061622 G allele carrier and history of smoking conferring a significantly higher risk (OR 5.42, 95% CI 2.48–11.84, p < 0.0001) compared with the TT genotype and no history of smoking. The AP due to interaction between the TNFRSF1B rs1061622 genotypes and smoking was estimated to be 0.49 (95% CI 0.7–0.92, p = 0.023) [7]. This measure was not equal to zero, suggesting the existence of a biological (additive) interaction Meanwhile, the multiplicative interaction measure was not significant. Thus, the results suggest evidence for additive but not multiplicative interaction.

Boudigaard et al in their study with Denmark Cohort (Danish Occupational Cohort/National Patient Registry N = 255 male/1821 female SLE, control = 1,541,505 male/1,470,769 female Danish residents with 1 + year of gainful employment 1977–2015) analyzed respirable crystalline silica exposure for each year of employment based on SYNJEM job exposure matrix [8]. Discrete time hazard models were used using logistic regression adjusted for age and calendar year of follow-up. Mean exposure per 50 µg/m3-years: males: IRR = 1.09 (1.01, 1.17) females: IRR = 1.04 (0.89, 1.22)

Ying D et al in their US Cohort study recruited veterans from the Army, Navy, Air Force, or Marine Corps, 63% White,12% female(N = 467 SLE, = 722,352) potential participants identified through 30 September 2018. Inorganic dust exposure was estimated using military occupation codes Inverse association between military dust exposure and SLE [9]. Generalized estimating equations were adjusted for age at first encounter at a US Veterans Affairs medical center or outpatient clinic, race/ethnicity, sex, and smoking status and accounting for correlation between members of the same branch of service. Military dust exposure: OR = 0.81 (0.76, 0.88).

In contrast to RA, dust exposure was statistically protective for SLE (OR = 0.81; 95% CI = 0.76-0.88),with this statistically significant protective association being present in those with 2 years to 4 years and 4 years to 8 years of service but not in the those with more than 8 years of service. The point estimate was even larger among women, with dust being statistically protective up to 8 years. In men, dust was not statistically protective

Jung CR (10) in their Taiwan Cohort(Longitudinal Health Insurance Database 2000) had 50% female(N = 1292 incident SLE through 2010,N = 682,208 persons aged 18–70 at baseline (1 January 2001) who fit inclusion criteria). Air pollution—ground level concentrations of CO, NO2, O3, and SO2 based on individual residential addresses, using land use regression models at 1 km spatial resolution. Associations between air pollutants (CO, NO2, PM2.5) and SLE were estimated. Mixed effect Cox proportional hazards regression was adjusted for age, sex, socioeconomic status, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, hyperlipidemia, and hypertension..There were positive associations of SLE with exposure to a 9.76 ppb increase in nitrogen dioxide (NO2), a 0.20 ppm increase in carbon monoxide (CO), and a 10.2 µg/m3 increase in fine particles (PM2.5) (HR = 1.21, 95% CI: 1.08-1.36, HR = 1.44, 95% CI: 1.31-1.59, and HR = 1.12, 95% CI: 1.02-1.23, respectively). Additionally, we observed negative associations with ozone (O3) and sulfur dioxide (SO2). According to the exposure-response relationships, exposure to NO2 between 28 and 38 ppb, exposure to CO above 0.6 ppm, and exposure to PM2.5 between 18 and 46 µg/m3 were positively associated with SLE.

Zhu X et al recruited from Huashan Hospital, Shanghai, China, and it was a case control design with : 100% Han Chinese, 68% female (N = 421 SLE, ACR criteria for diagnosis N = 425 control) [10,11]. Association between Current smoking and IL-33 gene polymorphisms was assessed. Logistic regression was adjusted for age, gender, BMI, and alcohol drinking and the equation - OR = 1.62 (1.21, 2.05) rs1929992 × current smoking: p = 0.001

Bae S C et al in USA based case control study (North Americans of

European descent) recruited 1311 SLE from five study collections with DNA samples, 4 + ACR criteria with 1783 control two-sample Mendelian randomization (MR) analyses were done using the inverse-variance weighted (IVW), weighted median, and MR-Egger regression methods on publicly available summary statistics datasets using two vitamin D level genome-wide association studies (GWASs) as exposure and SLE and RA GWASs on people of European descent as outcomes.No evidence of a causal association between vitamin D level and risk of SLE (beta = 0.032, SE = 0.119, p = 0.789; beta = 0.233, SE = 0.274, p = 0.552; beta = 0.054, SE = 0.125, p = 0.665; respectively) [12].

Castro Webb et al used multivariable (MV) Cox regression models to estimate HRs and 95% CIs for macronutrients, carbohydrates, proteins, total fats, PUFAs, ω-3 fatty acids, ω-6 fatty acids, MUFAs, saturated fats, trans fatty acids, Alternative Healthy Eating Index score, vegetable/fruit and meat/fried food dietary patterns, and a reduced rank regression (RRR)-derived dietary pattern in relation to SLE risk [13]. MVHRs and 95% CIs for the highest quintile of intake versus the lowest were HR: 1.96, 95% CI: 1.02, 3.67 for carbohydrates; HR: 0.66, 95% CI: 0.37, 1.18 for protein; and HR: 0.54, 95% CI: 0.28, 1.01 for total fats. MUFAs, saturated fatty acids, and trans fatty acids were significantly associated with a lower risk of SLE. The high intake of carbohydrates and low intake of total fats were associated with higher risk of SLE. These results were confirmed using substitution and RRR analyses. In particular, we identified a dietary pattern high in fruits, orange juice, and sweetened soft and fruit drinks and low in margarines and butter, red and processed meats, fried chicken, poultry, and eggs to be associated with risk of SLE.

Cui Ze et al studied 673 patients with SLE (diagnosed according to the American College of Rheumatology 1997 updated classification criteria) were matched by age, sex, and race (first 3 genetic principal components) to 3,272 control subjects without a history of connective tissue disease. Smoking status was classified as current smoking/ having recently quit smoking within 4 years before diagnosis (or matched index date for controls) versus distant past/ never smoking. In total, 86 single-nucleotide polymorphisms and 10 classic HLA alleles previously associated with SLE were included in a weighted genetic risk score (wGRS), with scores dichotomized as either low or high based on the median value in control subjects (low wGRS being defined as less than or equal to the control median; high wGRS being defined as greater than the control median) [14].

A high wGRS (odds ratio [OR] 2.0, P = 1.0 × 10−51 versus low wGRS) and a status of current/recent smoking (OR 1.5, P = 0.0003 versus distant past/never smoking) were strongly associated with SLE risk, with significant additive interaction (AP 0.33, P = 0.0012), and associations with the risk of anti-dsDNA+ SLE were even stronger. No significant multiplicative interactions with the total wGRS (P = 0.58) or with the HLA-only wGRS (P = 0.06) were found

Refai et al study sample consisted of 29 female SLE patients, and 27 healthy controls, who matched the cases on age and parity. The multivariate stepwise logistic regression model revealed that five factors showed significant association with SLE, namely living near agricultural areas, passive smoking, blood lead levels ≥ 0.075 mg/L, and exposure to sunlight (OR =58.556, 95% CI =1.897-1807.759, OR =24.116, 95%CI =1.763-329.799, OR =18.981, 95%CI =1.228-293.364, OR =9.549, 95%CI =1.299-70.224 respectively). Whereas walking or doing exercise were significantly protective to SLE (P =0.006) [15].

Epigenomic and Exposome Interaction

Ray et al hypothesized that expression of genes susceptible to DNA methylation in T cells from SLE patients may be more prevalent in low-micronutrient conditions than in healthy T cells [16]. They cultured CD4+ T cells from lupus patients PHA-stimulated in culture media with normal or low levels of B6 and B12 vitamins, methionine, folate and choline, and then measured expression of CD70, perforin and KIR. It should be noted that KIR, perforin and CD70 genes are usually hypermethylated and overexpressed in SLE. The authors observed that CD4+ T cells from SLE patients cultured in low levels of supplements exhibited an increase in these methylation-sensitive genes. In conclusion, SLE patients may pay attention to their nutrition to avoid low levels of methyl donors and DNMT activity, preventing lupus flares and onsets, especially older people with more diet deficiencies. Lupus, a prototype complex autoimmune disease, also needs a detailed ‘interactome’ approach for identifying populations at risk, prognostication and new therapies. Interactome-based studies are comparatively less in number in lupus especially exposome -genome - epigenome interaction.

Unmet Needs

The environmental and population diversity is significant throughout the World, exposome study will help to identify potential risk factors and it might also inform us about modifiable risk factors and a preventive model of lupus development irrespective of genetic background This study will help to identify risk allele and epigenetic modifications created by exposomes causing lupus flare in lupus. New therapies based on exposome-genome-epigenome interaction can be postulated and idea of non-pharmacological therapy with prevention of modifiable risk factors can be generated

Conclusion

It is worth noting that while some studies have explored the interactions between the exposome, genome, and epigenome in SLE, the number of interactome-based studies in this context is relatively limited. Given the potential insights and benefits that such studies can provide, further research in this area is warranted. By adopting an interactome-based approach and leveraging advances in technology and data analysis, we can improve our understanding of SLE, identify novel therapeutic targets, and potentially develop more effective treatments for this complex autoimmune disease.

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