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Determining the Impact of MeCP2/DNMT1 Imbalance in Epigenetic Dysregulation

By investigating key DNA methylation regulators, I will determine if their misregulation is sufficient to cause defective DNA maintenance methylation and dysfunctional helper T cells as seen in lupus.

Systemic lupus erythematosus (SLE) or lupus is a chronic auto-immune condition where the immune system attacks healthy cells and tissues.

Lupus is a chronic auto-immune condition where the immune system attacks healthy cells and tissues.

No two cases of lupus are the same and symptoms can range in severity, duration and onset.

Kaul A, Gordon C, Crow MK, Touma Z, Urowitz MB, Van Vollenhoven R, et al. Systemic lupus erythematosus. Nat Rev Dis Prim 2016 21

Lupus is among the leading causes of death in young females.

Cumulative mortality* of incident systemic lupus erythematosus (SLE) cases diagnosed during 2002–2004, by black/white race

Lupus mortality rates remain high (10–15%) in minority women (45–64)

Lim SS, Helmick CG, Bao G, Hootman J, Bayakly R, Gordon C, et al. Racial Disparities in Mortality Associated with Systemic Lupus Erythematosus—Fulton and DeKalb Counties, Georgia, 2002–2016. <https://my.clevelandclinic.org/health/symptoms/23163-lupus-rash>

Epigenetic Dysregulation leads to SLE Pathology

SYSTEMIC INFLAMMATION → T CELL DYSFUNCTION → LOSS OF DNA METHYLATION → Aberrant gene expression

Loss of DNA methylation leads to aberrant gene expression. This triggers an inflammatory T cell phenotype responsible for chronic inflammation central to SLE pathogenesis.

MeCP2 and DNMT1 Imbalance may induce loss of DNA Methylation

In normal T cells, MeCP2 and DNMT1 maintain DNA methylation.

In Lupus T Cells, an imbalance of MeCP2 to DNMT1 may disrupt DNA methylation maintenance.

Epigenetic Engineering to Understand MeCP2/DNMT1 Dysregulation in Lupus

Orthogonal CRISPR Transcriptional System

Simulate Response to Environmental Triggers

Synthetic Maintenance Methylation Circuit

Future Outlook

- Establish a causal link between MeCP2/DNMT1 and T cell dysfunction in lupus.
- Reveal epigenetic events that precede lupus flare and enlighten how we view disease activity.
- Better inform drug target development and treat lupus flares.

