



Introduction

Systematic Lupus Erythematosus

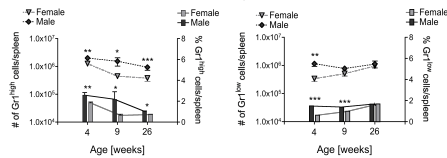
- Autoimmune disease characterized by production of anti-nuclear autoantibodies (ANAs)
- Higher prevalence in women, 9:1 female to male ratio

Mouse Model of SLE

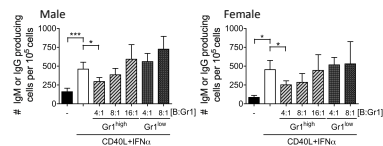
- F1 hybrid of New Zealand Black (NZB) and New Zealand White (NZW) mice (BWF1)
- Spontaneously develop a lupus-like disease with elevated ANAs, glomerulonephritis, proteinuria and renal failure
- Female predominance: 100% of female mice develop disease, only 30% of male mice

Gr1+ Cells

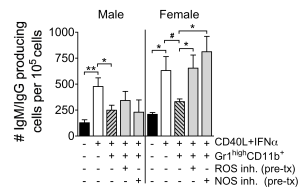
- Immunosuppressive population of myeloid origin
- First described in cancer models as tumor promoting cells that suppress anti-tumor responses
- Identified in lupus as Gr1⁺CD11b⁺ cells, play a protective role in lupus pathogenesis



Male BWF1 mice have higher levels of Gr1⁺ cells than female mice



Gr1⁺ cells suppress B cell differentiation *in vitro*



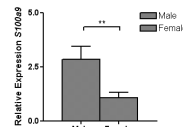
Female Gr1⁺ cells suppress B cells through ROS/iNOS

Experimental Question

What mechanism do male Gr1⁺ cells from BWF1 mice use to suppress B cell differentiation and antibody response?

S100a9 Protein

- MDSC have been shown to utilize S100a9 as a suppressive mechanism in cancer studies
- S100a9 is a 14kD protein that regulates inflammation and recruits leukocytes during an inflammatory response
- S100a9 has been shown to have a chemotactic effect on Gr1⁺CD11b⁺ cells

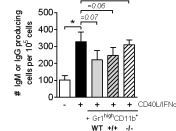


S100a9 is overexpressed in male BWF1 mice as compared to female

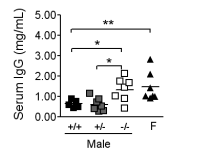
Hypothesis

We hypothesize that Gr1^{hi}CD11b⁺ cells from male BWF1 mice use S100a9 as an immunosuppressive mechanism, inhibiting antibody response and protecting from disease development.

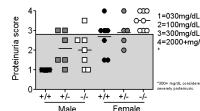
Data/Results



S100a9 mediates B cell suppression by Gr1⁺ cells *in vitro*



S100a9 KO mice have significantly higher circulating IgG levels



S100a9 KO mice trend towards higher levels of proteinuria

Conclusions/Future Directions

Male BWF1 mice have higher levels of Gr1⁺CD11b⁺ cells and higher levels of S100a9 than female counterparts

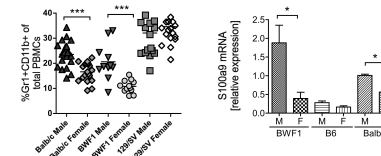
S100a9 plays an essential role in B cell suppression and antibody production by Gr1⁺CD11b⁺ cells in male lupus-prone BWF1 mice

Gr1⁺ cells from S100a9 KO mice do not suppress B cells, have higher antibody production, and increased proteinuria

The suppressive mechanism of S100a9 appears to be significantly more active within male mice, suggesting it may be intrinsically involved in the protective mechanism of testosterone

Future Directions

- Do Gr1⁺ cells function similarly in non-autoimmune mice as they do in lupus-prone BWF1 mice?
- Is the protective function of Gr1⁺ cells restricted to male BWF1 mice or is it a protective mechanism of testosterone?
- Is the suppressive role of S100a9 intrinsic to male lupus-prone BWF1 mice or does it play the same function in non-autoimmune mice?



Acknowledgements

Special thanks to researchers at the Department of Immunology, Lerner Research Institute through the Cleveland Clinic Foundation. Thanks to Trine N. Jorgensen, PhD for advising and Dr. F Paul Doerder for guidance.

A very special thanks to Dr. Leah Gold, COF and STEM for this opportunity.

References

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- Trigunaita, A., A. Khan, E. Der, A. Song, S. Varikuti, and T. N. Jorgensen. 2013. Gr-1(high) CD11b⁺ cells suppress B cell differentiation and lupus-like disease in lupus-prone male mice. *Arthritis Rheum.* 65: 2392-2402.