Persistent Stress During Pregnancy Influences Thymic Development in Murine Offspring

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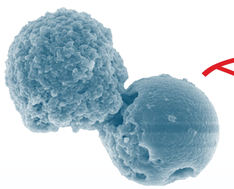


Abstract

Thriving in spaceflight presents a unique challenge for humans. Exposure to extreme socioenvironmental stressors, such as altered gravity, ionizing radiation, and social isolation all can affect human biology. It is understood that physiological and psychological stress can disrupt gestation and reproduction processes in humans, as well. Using the mouse model, Chronic Unpredictable Mild Stress (CUMS), we can assess the influence of socioenvironmental stress on various biological systems, including the relationship between immune and reproductive systems. The thymus is an important gland involved in early life immune development and is sensitive to external factors that can disrupt T cell receptor diversity and antigen specificity. Due to this, we assessed retrospective, open-sourced data from GeneLab Open Science Directory (OSD-287). This data consists of thymic transcriptomes of two-day old pups born to dams that were exposed to CUMS for three-weeks. We aim to identify thymic immune pathways and activities that are involved in T cell development. Therefore, we hypothesize that CUMS exposure in dams will impair antigen presentation pathways and T cell tolerance processes in the thymus of pups. In brief, this project will identify processes that engage T cell activity in pup thymic development and examine the consequences of socioenvironmental stress in gestation.

Background

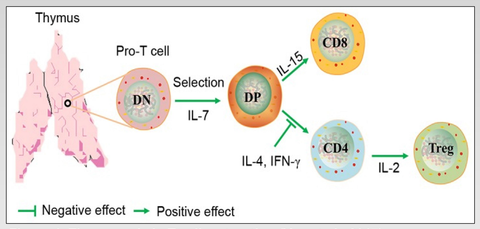


Figure 1. Thymus role in T-cell maturation (Yan et al., 2017).

- The thymus is the center of T cell differentiation and maturation.
- Defects in thymic efficiency can lead to immune issues later in life: such as autoimmunity or immunodeficiency.
- The thymus involutes after year one in humans and around 4-6 weeks in mice - smaller and less effective at T cell production.

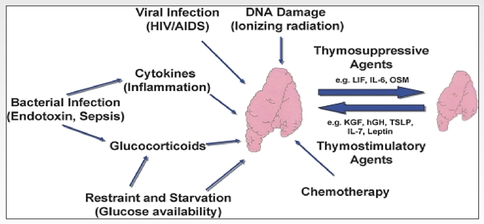


Figure 2. Thymic involution triggered by chronic stress response (Gruver, Sempowski, 2008)

-Stress-induced thymic involution **reduces** thymic size

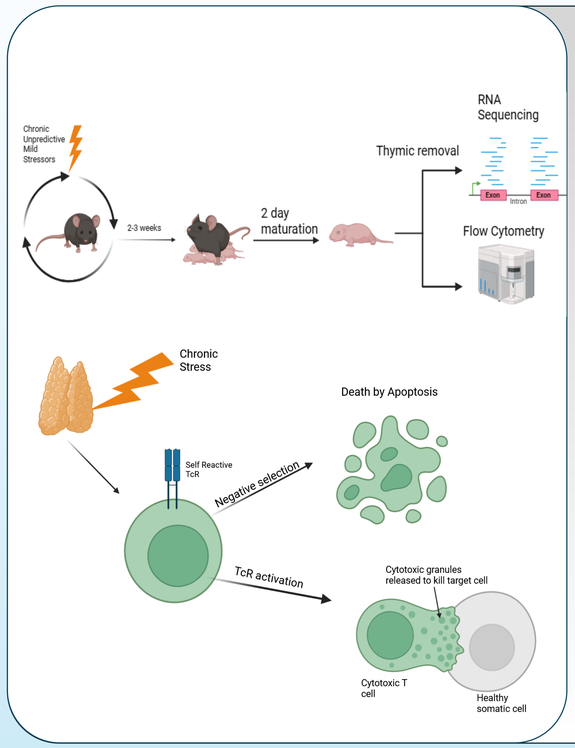
Reduced thymic size during development/early life may lead to:

- Decreased T cell output.
- Reduced response time to environmental pathogens.
- Cortisol resistant immune cells.

Collectively these may result in severe immunodeficiency, and poor control of inflammatory responses at birth, that may extend into maturity.

Relevance

- High levels of persistent stress early in life may be a contributing factor leading to autoimmune disorders developing later in life. (Dube, et al, 2009).
- Chronically high exposure to cortisol may lead to prolonged inflammation and **thymic involution**. Weakening the immune system over time.
- Chronic inflammation can cause cellular damage, attracting the immune system to generate a response against self-tissues (Yoon, Jun, 2005).



Results

Generated from Fonte et al., 2018

Figure 3. Experimental methods performed for CUMS exposure.
Pregnant dams were exposed to several socioenvironmental stressors, up to 18 hours, with 6-hour intervals of no stress. They would be cycled randomly until pups were born. Two-days post-birth pup's thymuses were harvested for RNA sequencing and flow cytometric analysis.

CUMS socioenvironmental Stressor:

- Reversed day/night cycles
- isolation
- confinement
- soiled cage
- limited food

Figure 4. Self-reactive TcR (Minor Repertoire) may lead to autoimmunity.
The experiment has shown that there is a **significant** increase in CDR3 expression on minor repertoires of the TcR. However, socioenvironmental stress does not affect VDJ recombination, or thymocyte maturation.

Potential Outcomes:

-Lower T cell population.
-Persistent inflammation may lead to autoreactive receptor reactivation.

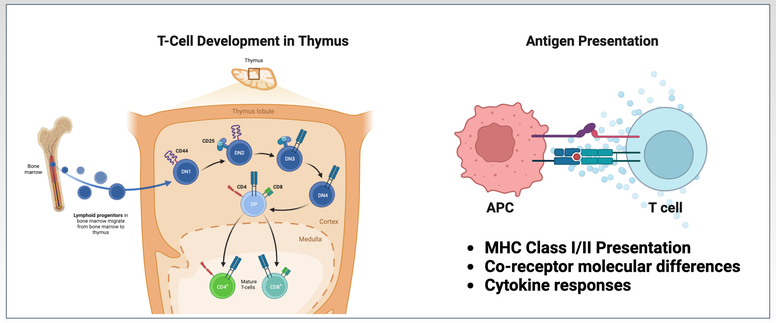
Unanswered Questions

1. What happens to the immune status of pups in maturity to adults?
2. Do increased levels of self-reactive T cells influence overall T cell populations and therefore responses?
3. What other receptors, or costimulatory molecules may have been affected by CUMS, what are these implications?

GeneLab is an Open-Source Database (OSD) for aerospace related biological data. Re-analyzing the RNA-sequencing data from Fonte et al., 2018 manuscript, Open Science Directory (OSD)-287 to preforming a broader analysis on the thymic expressional data.

Next Steps

We hypothesize that CUMS exposure in dams will impair antigen presentation pathways and T cell tolerance processes in the thymus of pups.



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