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Immunological changes at puberty drive increased mortality from endotoxemia in mice

Sepsis is a complex and deadly syndrome in which the body's response to infection malfunctions and loses the ability to resolve inflammation properly. This loss manifests in a variety of ways, ranging from organ-damaging inflammation to immune system suppression and susceptibility to secondary infections. Despite decades of research, there is still no cure for sepsis and its pathogenesis remains largely a mystery. A deepened understanding of the factors that rebalance the immune system after infection, versus those that do not, may be the key to finding a cure for sepsis.

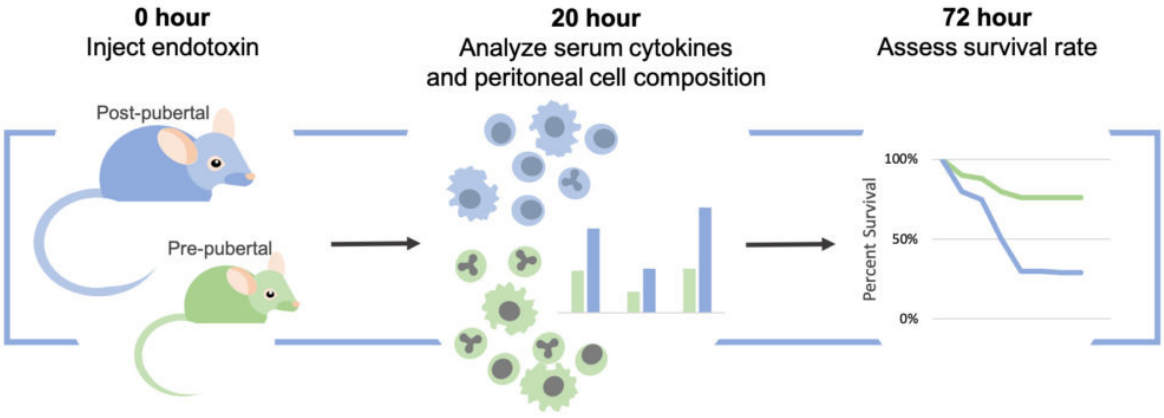

Fig. 1.

Interestingly, epidemiological studies suggest that, when compared to adults, children exhibit decreased mortality in multiple conditions that typically involve the dysregulation of the immune system. Along with sepsis, this trend extends to infections with pandemic influenza strains, tuberculosis, and Ebola, among others. This survival advantage is particularly apparent in pre-pubertal children and in some examples, seems to disappear with the transition through puberty.

To explore this phenomenon experimentally, we established a simple mouse model of pre-pubertal resistance to sepsis using intra-peritoneal injection of endotoxin. Endotoxin, or more specifically, lipopolysaccharide, is a component of the gram-negative bacterial cell wall that rapidly initiates an intense inflammatory response, which can progress into organ failure and death. We used this endotoxin injection or "endotoxemia" model, to characterize the immune responses of pre- and post-pubertal mice and to explore the possible mechanisms differentiating them.

Seventy-two hours following endotoxin injection, we determined that female pre-pubertal mice exhibited significantly greater survival (76%) than post-pubertal mice (29%). Age-associated differences in the inflammatory response only became evident twenty hours following endotoxin injection. At this time, post-pubertal animals exhibited higher expression of many cytokines (IFN-γ, IL-5, IL-13, IL-15, and IL-17), growth factors (LIF and VEGF), and chemokines (eotaxin, MCP-1, and MIP-2) in comparison to pre-pubertal

mice. Along with prolonged elevation of serum cytokines, post-pubertal mice showed differential recruitment of immune cells into the peritoneal cavity, in particular a lower percentage of infiltrating neutrophilic (Ly6G+Ly6C+) versus monocytic (Ly6G−Ly6C+) cells.

We next investigated how pubertal status influenced the differential mortality of pre- and post-pubertal animals in response to endotoxemia. Treatment of pre-pubertal mice with estrogen prior to endotoxin injection significantly expedited puberty onset, as measured by vaginal opening (an early indicator of female mouse puberty), and increased mortality from endotoxemia compared to vehicle-treated mice (60% vs. 27%). Additionally, the prevention of puberty by pre-treatment with the gonadotropin releasing hormone agonist, leuprolide, led to improved survival compared to age-matched controls (80% vs. 35%).

Before treatment with endotoxin, pre- and post-pubertal mice exhibited similar resident peritoneal cell profiles, (as assessed by flow cytometry), except for a significantly higher percent composition of B and CD4+ T cells in post-pubertal mice. To determine whether the pre-pubertal peritoneal cell composition was driving their resistance to endotoxin, we used adoptive transfer to see whether resident pre-pubertal cells could improve survival in post-pubertal animals. Indeed, adoptive transfer of peritoneal cells from pre-pubertal mice into recipient post-pubertal mice, increased survival from endotoxemia, while transfer of post-pubertal cells or vehicle did not. These findings indicate that the pre-pubertal resistance can be transferred to a post-pubertal animal and that peritoneal immune cells are intimately involved.

These data establish a model for studying childhood resistance to mortality from endotoxemia, demonstrate that estrogen is responsible for an increased susceptibility to mortality after puberty, and identify peritoneal cells as mediators of pre-pubertal resistance. By studying the mechanisms that drive pre-pubertal resilience to mortality, we hope to elucidate the changes in the immune response that begin during the pubertal transition and identify new ways to treat sepsis.

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Publication

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