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Viraspillai J., Samyuktha R.

COMPENSATORY MECHANISMS FOLLOWING IMMUNOSUPPRESSION DUE TO THYMIC INVOLUTION

Tutor: PhD, associate professor Kochubinski V.V.
Department of Microbiology, Virology, Immunology
Belarusian State Medical University, Minsk

Thymus is a primary lymphoid organ located in the mediastinum which responsible for generating self-tolerant and immunocompetent T cells, which has two compartments, the epithelial space and perivascular space. This micro-environment is a specialized cellular space comprised epithelial cells, myoid cells and accessory cells derived from bone marrow. This environment is important for the differentiation, maturation and selection of T lymphocytes. Thymic involution (TI) refers to the natural process of shrinking and loosing ability to produce functional cells as a person ages or any chronic reasons. Even though, it is a normal part of ageing process, the impact of this huge, that is role of age related disease, infections and immune system recovery after special condition like immunosuppression

Some scientists divide this system as two major stages, those are early phase (growth-dependant TI) and late phase (age-dependant TI) (Aw & Palmer, 2012). In early life, it is vital to maintain high thymic activity and produce broad T- cell receptor (TCR) diversity to protect against infections (Aw & Palmer, 2012). Once the T- cell repertoire is established, it may be good for the organism to reduce thymic activity and redistribute energy to other organs. But most important process is late phase. So in the late phase, how TI happens, in humans TI starts after the age of 1 and continues 3% for every year (George & Ritter., 1996). In that period, some main events happens, primarily, cortical and medullary thymic epithelial region structure becomes increasingly less reticular and less globular, definite cortical- medullary junction is lost (Aw et al., 2008), thymic epithelial space contraction, perivascular space augmentation, reduced production of the thymopoietic cytokine IL-7 (Ortman et al., 2002) ,proportion of mature cortical thymic epithelial cells (cTECs) and inter typical TECs are increased, decline in E2F3 transcriptional targets (Wu et al., 2018), (factor that mediate cell proliferation and cell-cycle regulating genes), because of adipocyte increases which inhibit thymic function through adipocytokine (Dixit., 2010) and by the global transcriptome analysis (Griffith et al., 2015) revealed in stromal cells reduced level of catalyses leads to increase of peroxides in thymus and cause oxidative stress which leads to thymic atrophy. And some molecular negative regulators are Axin, IL- 6, IL- 1β and follistatin which exhibit increased activity with age. In addition, obesity and sex hormones exacerbate age-related thymic involution.

Humans experience a decline in thymic output as they age. However, the number of naive T cells decreases less dramatically than the number of thymocytes (developing T cells in the thymus). This suggests mechanisms beyond thymic output play a role in maintaining the naive T-cell pool in humans and naive T cells are extremely long-lived, with CD4+ naive T cells living ~6 years and CD8+ naive T cells living ~9 years. This is about 40 times longer than naive T cells in mice (J. Miller., 2015). However, this shift leads to reduce the diversity of the T-cell receptor (TCR) repertoire makes holes in this repertoire, leads to only fewer cells can only capable to identify new antigens and this leads to new diseases. Studies estimate that up to 90% of daily naive T-cell production in adult humans comes from peripheral division, while only about 10% originates from the thymus (Kvell et al., 2010). T-cell receptor excision circle (TREC) declines significantly in naive T cells during aging. TRECs are markers of thymic origin, as they are generated during T-cell development in the thymus and not replicated during cell division. A decline in TRECs suggests that peripheral division (division of naive T cells outside the thymus) becomes more important in maintaining the naive T-cell pool in humans as thymic output decreases. Children who had thymectomy at 5 years old, had recovery suggested, 1) Peripheral division of Naive T Cells 2) Thymic Regrowth (Zhou et al., 2016). Conclusion, even thymus involute, it at least give support for T cells compensation as well as with peripheral tissues as these studies suggests.