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Involvement of Restored Treg Cells in the Immune Pathogenesis of Parkinson's Disease (PD) Running Title: Immune Pathogenesis of Parkinson's Disease

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ABSTRACT

Neural regression with neuroinflammation and immune dysfunction through neurodegradative disorder is known as Parkinson's disease (PD). Parkinson's disease is a progressive degenerative neuronal disorder. In this disease, the continuous depletion of dopaminergic neurons and the existence of protein Lewy bodies are the key points of PD development. In PD patients, regulatory T cells (Tregs) are decreased in number and have an impaired proliferative capacity that affects the suppression of T-cell characteristics. The thymus involution decline in the functionality of T-cell development and consequently naïve T cells makes the immune system more vulnerable to losing its immune surveillance, increasing morbidity and mortality in aged individuals. The persistent process of thymic involution with age vigorously contributes to a progressive reduction in thymic output. Genomic damage, cellular senescence, and epigenetic alterations are the hallmarks of cellular or molecular damage in aging. Therapeutic potential for regeneration of the thymus would improve immunity. Some strategies and approaches have focused on cell-based approaches, technology based on organoid and scaffold modulating of endogenous and exogenous compounds to help in the thymus regeneration, and fabrication technologies that could be used as regenerative approaches. Last but not least the pluripotent stem cell therapies.

INTRODUCTION

Neural regression with neuroinflammation and immune dysfunction through neurodegradative disorder is known as Parkinson's disease (PD). Parkinson's disease is a progressive degenerative neuronal disorder. In this disease, the continuous depletion of dopaminergic neurons and the existence of protein Lewy bodies are the key points of PD development. Increased microgliosis along with dysfunction of the peripheral immune were also indicated by several reports in the development of PD (Balestrino & Schapira, 2020). Prevalence showed that it is the second chronic progressive neurodegenerative disease after Alzheimer's, with environmental and genetic factors that interact to develop it in older age (Miri *et al.*, 2020) (Goldman, 2019). In PD patients, regulatory T cells (Tregs) are decreased in number and have an impaired proliferative capacity that affects the suppression of T-cell characteristics. In animal models of PD, restoring Tregs and their suppressive function reduces disease-associated inflammation and provides neuroprotection.

Similarly, in the field of cancer- a disease no less dangerous than Parkinson's disease (PD) - a Treg cell depletion restores and improves endogenous anti-tumor immunity. Accordingly, it becomes possible to promote regeneration and prevent the evolution to irreversible tissue damage by restoration of Treg cells. Thus, the restored Treg cells

help in the immunopathogenesis of Parkinson's disease (PD) (Thome *et al.*, 2021). In old age, thymus degradation is associated with decreased precursors of T cell output, which reduces individuals' activity in T cells. It increases susceptibility to infection and is prone to autoimmune disease and cancer.

Thymic involution is the intense situation in which ubiquitous change is observed in the aging immune system, but the mechanisms underscore this process are still unclear (Barbouti *et al.*, 2020). The prevalence of PD has increased day by day. Approximately 2.5 million individuals suffered it in 1990, while the prediction shows it will increase three-fold to 17.5 million in 2040. Reduces neuroprotection activities associated with environmental parameters, i.e., pollution, smoking, and boosted exposure to industrial byproducts (Schwab *et al.*, 2020). Usually, it affects the old aged individual more than the adult once. Because it depends upon the immunological status of humans. In old age, the body's system becomes weaker timely, so the immune system is also affected by the side effects of other pathological conditions such as hypertension, stroke, and other cardiovascular disorders (Mas-Bargues *et al.*, 2021). The thymus gland begins to atrophy (shrinks) until we have little or none left. T-cells migrate towards the thymus to mature from the bone marrow because it is the primary lymphoid organ.

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It is also involved in the development to improve the efficiency of T-lymphocytes or T cells (Knight, 2021). Persistent age-associated atrophy is found in the thymus gland in which loss of thymic epithelial space (TES), i.e., thymus involution or atrophy, leads to inhibition of thymic output (Rezzani *et al.*, 2020). It was represented by its role in developing T-lymphocytes or T cells, an extremely important type of white blood cell. T cells protect the body from potentially deadly pathogens like bacteria, viruses, and cancer. Such a regulatory role driven by T cells causes dysregulation in immune cells (Varadé *et al.*, 2021). The dysregulated Immune cells lead to a pro-inflammatory tumor microenvironment and promote the secretion of growth factors, i.e., chemokines and cytokines/proteinases.

Additionally, the Intercellular communication between cancer and immune cells plays a key role in modulating the immune response, promoting cell migration, proliferation, and tumor progression (Schulz *et al.*, 2019). The state of chronic thymus involution in aged individuals creates a weaker immunity through a great decline in the functionality of T-cell development and consequently naïve T cells. This makes the immune system more vulnerable to losing its immune surveillance, increasing morbidity and mortality (Schwab *et al.*, 2020).

Significance of Thymus in the Human Body

Thymus, located right behind the collarbone, is the essential part of the immune system. In the thymus, naïve T immune cells develop through undifferentiated thymocytes specializing in specific pathogens or cancer cells. T cells serve a potential role in regulating the immune system. It has been important that the size of thymus reduces progressively with age, termed thymic involution (Barbouti *et al.*, 2020). The thymus's immune benefit produces a class of immune cells called T lymphocytes. These cells complement the B cells to constitute the adaptive immune system. Humans produce fewer and fewer T cells as humans age, and some recent literature reported that humans might not even produce any newer T cells after age 60 (Park *et al.*, 2020). The persistent process of thymic involution with age vigorously contributes to a progressive reduction in thymic output. Humans become more susceptible to cancer and infectious diseases in old age as their immunity weakens (Wiertsema *et al.*, 2021).

Predisposing Factors of Thymic Involution

The shrinkage of the thymus in old age, this phenomenon is known as involution. An ancient and evolutionarily conserved process showed that thymic involution occurred in many vertebrates (Rezzani *et al.*, 2020). Thymic aging is marked by lowered production of (new) naïve T cells and adipose tissue instead of lymphosarcoma thymic zones (Cakala-Jakimowicz *et al.*, 2021). Literature shows that thymus shrinkage is an age-dependent program. The infiltration of adipocytes (fat cells) is initiated in puberty or earlier and will take over in middle age. Age changes

in the thymus into fatty tissue from a primary lymphoid organ (Velardi *et al.*, 2021). Besides fat deposition, many other factors of age-associated changes may trigger thymic involution. Firstly, the decrease in bone marrow output is the source of hematopoietic stem cells (HSC). This comprised of T cell progenitors anonymously enter the blood circulation and relate thymic epithelial cells to get matured, defined as the developmental program. The decline was observed in T-cell progenitor cells and hematopoietic stem cells by age (Liu *et al.*, 2020). Second fibrosis, by the age of thymopoiesis replaced by fibroblasts after signaling by specialized thymic epithelial cells. Fibrosis is also observed in various organs, i.e., the liver, kidney and heart, as a common aging signature (Borgoni *et al.*, 2021). Thymic involution consists of a two-stage process, growth-dependent thymic involution during puberty and age-dependent thymic involution (Sekai *et al.*, 2019).

Formation of Intrathymic T Cell Receptors (TCRs)

The T cells mature in the thymus, migrate from the bone marrow as pre-T cells, and pass through the thymus. They form their T cell receptors (TCRs) with their two chains (α and β). These TCRs give the T cell its specificity through a process of genetic recombination. They go through positive and negative selection in the thymus. So, if a TCR binds to self too strongly (they would cause autoimmunity), they are deleted. If they cannot bind self-enough, they would be unable to make antigen recognition bound by MHC molecules, which is typically required for T cells then they are also deleted. Those that can loosely bind MHC but not so strong that they would be self-reactive mature T cells reach the secondary lymphoid organs before they can remain in the blood circulate (i.e., spleen, lymph nodes, etc.) (Smith & Göbel, 2022).

Intrathymic Integration of T Cell Migration and Thymocyte Differentiation

The thymus gland is necessary for producing T lymphocytes, central to cellular immunity, humoral immunity, and some of the body's nonspecific defenses. Chemokine receptors, such as CC-chemokine receptor 7 (CCR7), CCR9 and CXCR4 are responsible for the recruitment and entry of bone marrow-derived T lymphoid cell progenitors, called thymocytes. Two events for the maturation of thymocytes were reported: the rearrangement of the gene of the TCR and association with coreceptors CD4 and CD8 (Granadier *et al.*, 2021). Thymocytes' progress depends upon three developmental stages with an expression of the CD4 and CD8 coreceptors. Double-negative (DN) thymocytes do not express CD4 and CD8 in T-cells after attaching with coreceptors CD4 and CD8. TCR consists of α and β subunits having alternate sequences. This variation shows the randomization of gene segments and foreign antigen thymocytes, which can recognize as major histocompatibility complex (MCH) molecules (Cosway *et al.*, 2021). T cells increase their affinity by self-peptides

bound to (pMHC) for positive selection and peripheral survival. Mature TCRs with CD4 and CD8 coreceptors in the same cell are double-positive (DP) thymocytes. TCR-self-pMHC interactions promote DP thymocyte survival and convert it into a single positive (SP) stage. This outcome is called positive selection (Kisielow, 2019). Apoptosis is generated if TCR is not involved in self-pMHC, and high affinity (strong signaling) generated after self-pMHCs are known as non-selection and negative selection, respectively. (Srinivasan *et al.*, 2021) Self-MHC bond TCRs are restricted, mature and self-tolerant. When expressed CD4 or CD8, it becomes single positive (SP) thymocytes, also known as clonal selection (Helgeland *et al.*, 2020). The binding of CD4 or CD8 and TCR to the MHC molecule forms the TCR-CD3 complex through noncovalent interaction with CD3 γ , δ , ϵ , and ζ proteins of the intracellular domain. (Shah *et al.*, 2021) Expression of chemokine receptor CCR7 After positive selection tests of thymocytes as an additional requirement fulfill an in the medulla of the thymus. The medullary epithelial cells of the thymic produce CCR7 cytokines that enhance the negative selection of potentially autoreactive thymocytes. After development in the thymus, thymocytes migrate to the lymphoid organs through the bloodstream and are considered antigen-presenting cells. These lymphoid organs initiate protective immune responses in immunological challenges (Kadouri *et al.*, 2020).

Thymic Involution and Immune Econstitution

The thymus serves as the development of self-restricted and tolerated along with immunocompetent T cells. Thymus loses the characteristic of self-renewal. Therefore, the continuous replenishment of new T cell progenitors comes from the bone marrow. After proliferation series and stages of differentiation on the guideline of the specialized thymic microenvironment, these cells become Maturated. The anatomical structure of the human thymus gland is composed of the thymic epithelial space (TES) of the human thymus. Thymopoiesis continues on the nonhematopoietic perivascular area (PVS), including adipocytes, peripheral lymphocytes, and stroma. Reduce the efficiency of T-cell development and decreased migration of naïve T cells observed in aging characterized as chronic thymus involution (Sergi, 2020)

The progress on the therapeutic thymus restoration and peripheral immune reconstitution in adults. Restoring immunity in old age remains a challenge that needs further investigation. All older adults will be considered to have weak immune systems and reduced immunity due to vitamin D deficiency unless a supplement is taken. The weak immune function is associated with less responsive to drugs and more inclined toward infections in old individuals. Similarly, a study observed that the expression of activation markers and T cell memory phenotype distribution is affected by age, body fat content, and pathogen status throughout the Lifespan. (Mittelbrunn & Kroemer, 2021)

Inflammation and Treg Cell

Genomic damage, cellular senescence and epigenetic alterations are the hallmarks of cellular or molecular damage in aging (Ermolaeva *et al.*, 2018). Literature showed that imbalance protein and proteostasis conditions along with essential nutrient lacking were observed in aging-related diseases (Deng *et al.*, 2022).

According to De Cecco *et al.* 2019 chronic inflammation happens as self-antigens action due to pro-inflammatory reactions in aged persons (De Cecco *et al.*, 2019). Therefore, an imbalance of Th17/Treg cells was found to cause inflammation in aged people (Deng *et al.*, 2022). Previous studies showed that IL-6 also acts as a pro-inflammatory cytokine and helps to balance Th17/Treg cells in the human body but high serum TNF and IL-1 level imbalance the Treg cells in aged individuals (Pansarasa *et al.*, 2019). Reduced DCAF1 regulation was reported in Treg cells, which caused an imbalance rate of activation of T cells in the immune system of aged individuals compared to younger ones. Downregulation in DCAF1 ultimately increases the reactive oxygen species, directly affecting the interleukin 6 and interleukin 17 that imbalance the ROR γ ⁺ FOXP3 and caused Chronic inflammation by dysfunction immunity in aging (Guo *et al.*, 2020).

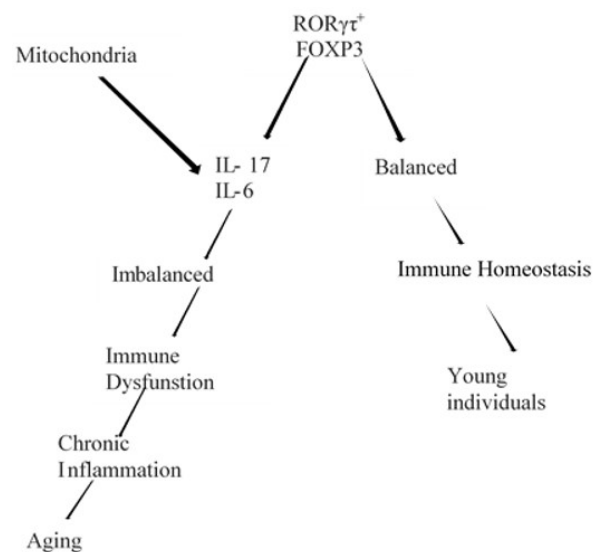


Figure 1: Chronic inflammation in aging due to imbalanced ROR γ ⁺ FOXP3

Approaches to Regenerate Thymus

Therapeutic potential for regeneration of the thymus would improve immunity. Some strategies and approaches have focused on cell-based approaches, technology based on organoid and scaffold modulating of endogenous and exogenous compounds to help in the thymus regeneration, and biofabrication technologies could be used as regenerative approaches. Last but not the least, the pluripotent stem cell therapies.

Literature showed that in vitro thymic epithelial

progenitors of humans could be generated through Embryonic stem cells (ESCs) with the help of Activin A, which can produce CD4+ and CD8+ T cells along with CD3 complex. Organoids technology extracts TECs by scaffolds through pluripotent stem cells (Table 1)(Sharma & Moroni, 2021). The progressive disease is

still untreated, but the cell replacement technique will be in consideration. Human pluripotent stem cell therapies are used as a regenerative strategy through straight differentiation for midbrain dopamine (mDA) neurons (Kim *et al.*, 2020), (Elsworth, 2020).

Table 1: Therapeutic Approaches to Regenerate Thymus.

Approaches	Mode	Action	References
OPDLL1system with HSCs	Synthesis of magnetic DLL1 ligands adds on VCAM-1 ligand.	Develop modification and enhance the Efficiency of T cells to make them diverse, functional, and produce cytokines	(Awong <i>et al.</i> , 2009)
Embryonic stem cells to Thymic epithelial cells	ESCs used to produce TEC	T cells are Diverse and responsive toward stimuli.	(Su <i>et al.</i> , 2015)
Reprogramming of thymic epithelial cells	Protocol to generate by FOXN1 transcription factor to increase cell count	The heterogeneous resemblance with endogenous ratio CD4:CD8	(Otsuka <i>et al.</i> , 2020)
Thymic epithelial cells generated from Scaffolding	Decellularized tissue by Synthetic or natural polymers	Bulk production with desired properties.	(Bortolomai <i>et al.</i> , 2019) (Barthlott <i>et al.</i> , 2021)
Thymic organoids (Artificial)	MS5-DLL1 cells cultured	Differentiation of T cell	(Seet <i>et al.</i> , 2017) (Montel-Hagen <i>et al.</i> , 2019)

CONCLUSION

Globally, PD is the most common chronic progressive neurodegenerative incurable disorder affecting elderly individuals over 65. The incurable PD, with its deteriorated motor function and devastating symptoms such as postural instability, bradykinesia, and quivering, suggests impairment of the patient's life. The Treg dysfunction in the pathogenesis of progressive Parkinson's disease may broadly improve our understanding of the pathology of this incurable disorder and assists in developing proper treatments for Parkinson's disease (PD) in the future. The possible CD4+CD25+Treg cells Treg dysfunction may be crucial in triggering and releasing dopamine chemicals (neurotransmitters) in the brain. Thus, suggesting that Treg dysfunction is associated with the pathogenesis of progressive Parkinson's disease. In this context, the possible contribution of CD4+/CD25+ regulatory T cells (Tregs) is to mobilize themselves to get rid of the PD pathology significantly. Therefore, the functional existence of highly regulated, adaptive immunopathogenic mechanisms will ultimately lead to developing future novel therapeutics for Parkinson's disease (PD).

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