The Recent Thymic Origin, Differentiation And Suppressive Mechanism Of Regulatory T Cells

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Nicholas Mabarrack

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"Education is not always empowering. It can create barriers to rewarding careers, demand sacrifices without promise of reward, and present opportunities nobody would want."

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Abstract

Regulatory T cells are a purported lineage of $CD4^+$ cells that inhibit the proliferation and effector functions of other T cells to prevent the development of autoimmune disease. However, little is known about how they arise, their lifespan and their patterns of recirculation. Furthermore, the mechanisms through which they inhibit other T cells remain unclear. In order to address these issues, we investigated the relationship between regulatory T cells and recent thymic emigrants (RTE) which are newly formed T cells released into the periphery from the thymus. The $CD25^+$ $Foxp3^+$ regulatory T cell subset was found to be closely associated with RTE, and generated the $CD25^-$ $Foxp3^+$ T regulatory T cell subset by unidirectional differentiation. This process was exploited to mature flow sorted $CD4^+$ $CD25^{bright}Foxp3^+$ T cells into $CD25^-$ $Foxp3^+$ T cells and determine that they retain their functional suppressive activity. The phenotype and physiology of the $CD25^+$ $Foxp3^+$ and $CD25^-$ $Foxp3^+$ regulatory T cell subsets were characterised and compared to conventional T cell subsets, revealing the differential expression of numerous key molecules. The high expression of CD62L and LFA-1 by $CD25^+$ $Foxp3^+$ regulatory T cells was consistent with both their relative enrichment within secondary lymphoid tissues and their sessile nature. The profile of adhesion molecules on the surface of $CD25^-$ $Foxp3^+$ cells suggested they may tend to localise to sites of inflammation other than the lamina propria, as they have a low expression of CD103 and CD62L, but high expression of LFA-1. However, $CD25^-$ $Foxp3^+$ regulatory T cells were found to selectively migrate into the intestinal mucosa, where they were enriched, and they also returned back to the thymus, suggesting they may constitute a tissue homing subset of regulatory T cells.

We explored the mechanism of regulatory T cell suppression, and found that regulatory T cells condition APC to reduce their ability to activate other T cells. Following the application of this system to differential gene expression microarray analysis, we identified several putative molecular targets of regulation including 10 novel predicted serine/threonine kinases, a novel four point-1, ezrin, radixin and moesin domain containing signalling molecule, the E2F transcription factor 5, and a CD163-like molecule.

Aging was found to negatively affect the productivity of the thymus, although it was found to be still generating new T cells into old age. While the number of thymocytes decreased with aging, the number of $Foxp3^+$ cells in the thymus was unaffected, possibly their preferential recirculation back to the thymus. The size of the peripheral T cell pool decreased with aging, and the proportion of $CD25^+$ $Foxp3^+$ regulatory T cells among $CD4^+$ T cells declined. However, the proportion of $CD25^-$ $Foxp3^+$ regulatory T cells increased with aging in the periphery. The conversion of $CD25^+$ $Foxp3^+$ regulatory T cells into $CD25^-$ $Foxp3^+$ T cells may compensate for the declining thymic output of $CD25^+$ $Foxp3^+$ regulatory T cells that occurs with aging, in order to maintain the regulatory T cell pool.

Abbreviations

APC	Antigen Presenting Cell
BrdU	Bromodeoxyuridine
BLAST	Basic Local Alignment Search Tool
CD	Cluster of differentiation
CFA	Complete Freund's Adjuvant
DC	Dendritic cell
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
FACS	Fluorescence activated cell sorting
FERM	Four point-1, ezrin, radixin and moesin domain
FITC	Fluorescein isothiocyanate
HEV	High endothelial venule
ICAM	Intercellular adhesion molecule
IDO	Indolaminde-2,3-dioxygenase
IFN	Interferon
IL	Interleukin
LAG	lymphocyte activation gene
LFA	Lymphocyte function antigen
MFI	Mean fluorescence intensity
MHC	Major histocompatibility
NCBI	National Centre for Biotechnology Information
PE	Phycoerythrin
PECy7	Phycoerythrin-Cy7
RAG	Recombination activation gene
RNA	Ribonucleic acid
RTE	Recent thymic emigrant
SRT	Synovium rich tissues
TCR	T cell receptor
TDL	Thoracic duct lymph
TGF	Transforming growth factor
Th	T helper
TNF	Tumour necrosis factor
TNFSF	Tumour necrosis factor superfamily
w/v	Weight per volume

Table of contents

Publications

Scientific Publications

Mabarrrack, N., Turner, N., and G. Mayrhofer (2008) “The recent thymicorigin, differentiation and turnover of regulatory T cells” Journal of Leukocyte Biology 84 (5) 1287-1297

Mabarrrack, N., and G. Mayrhofer “The suppressive mechanism of regulatory T cells” (manuscript in preparation)

Mabarrrack, N., and G. Mayrhofer “ The effect of aging on the thymic output of regulatory T cells” (manuscript in preparation)

Abstracts and conference presentations

Oral presentation by N.Mabarrack at the Proceedings of the Annual Scientific Meeting of the Australian Society of Medical Research, Adelaide, 2007 “The origins, lifespan and turnover of regulatory T cell subsets in rats” Nicholas H.E. Mabarrack and Graham Mayrhofer.

Oral presentation by N. Mabarrack at the 37th Annual Conference of the Australasian Society for Immunology, Sydney, 2007. “The origins, lifespan and function of regulatory T cell subsets in rats” Nicholas H.E. Mabarrack and Graham Mayrhofer.

Oral presentation by N.Mabarrack at the Proceedings of the Annual Scientific Meeting of the Australian Society of Medical Research, Adelaide, 2008 “The recent thymic origin, differentiation and turnover of regulatory T cells” Nicholas H.E. Mabarrack and Graham Mayrhofer.

Oral Presentation by N. Mabarrack at the Society of Leukocyte Biology conference in Denver, Colorado 2008 “The recent thymic origin, differentiation and turnover of regulatory T cells. Nicholas H.E. Mabarrack and Graham Mayrhofer.