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Commentary Open Access

Interleukin-21: A New Class of Thymopoietin for Immune Rejuvenation

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Abstract

More than two billion people will reach the age of 65 by 2050. Therefore, infectious disease/cancer-related morbidity and mortality of aged subjects is expected to rise. Several factors including impaired functions of body barriers and changes in microbial colonization contribute in increasing elderly susceptibility to infections and cancer. However, thymic involution, a hallmark of immunosenescence, is undoubtedly the principal component of this prominent problem. Although the thymus remains functional at older age, its pronounced diminished T-cell export rate is insufficient to sustain a competent naïve peripheral T-cell pool. Consequently, gradual dwindling in T-cell receptor (TCR) repertoire diversity takes place. As a result, the capacity of the elderly immune system to confer protection against cancer, acute/chronic infections or to respond to vaccination erodes. Therefore, there is an urgent need for the development of novel strategies aimed at: i) providing superior control of infectious diseases and cancer, and ii) improving responsiveness to all forms of immunotherapies.

Keywords: Thymopoiesis; Aging; Interleukin-21

Commentary

The thymus is unique due to its unparalleled capacity in supporting the *de novo* generation of naïve T cells [1-3]. Since the thymus lacks self-renewing progenitors, it heavily relies on sustained seeding with bone marrow-derived early thymic progenitors (ETPs) [4]. Unfortunately however, ETP numbers decline markedly with age due to increased apoptosis rates and reduced proliferative capacities [5]. This in turn leads to a diminished pool of double-negative (DN) and double-positive (DP) thymocytes triggering a negative impact on the delicate thymic stromal compartment (especially thymic epithelial cells-TECs) as the latter depends on cross-talk interactions with thymic progenitors for its sustained survival and function [6,7]. To compensate for such diminished thymic output, both homeostatic proliferation and increased T-cell life-span contributes to sustain the size of the peripheral T-cell compartment. As a result, aging peripheral T cells become highly exposed to extrinsic factors such as oxidative stress leading to a variety of intrinsic dysfunctionalities including: i) increased expression of several inhibitory/exhaustion receptors (PD1, LAG3, 2B4, and CD160); ii) alterations in cytoskeletal rearrangement and cell surface glycosylation, and iii) diminished formation of immune synapses with a 50% reduction in recruitment of signalling/adaptor molecules (Lck, ZAP-70, Fyn, LAT, Grb2 and Vav) [8-16]. Further investigations led to additional insights on a direct relationship between age-dependent decline of miR-181a levels in human peripheral naïve CD4 T cells and dampened TCR signaling, which ends-up adding an additional counterproductive layer of interference with normal responsiveness to exogenous antigens [11]. As these defects cannot be corrected at the single cell level, simulating thymopoiesis remains the only strategy capable of re-establishing a pool of "young" and diversified T cells free of intrinsic deficiencies and capable of competent immune responsiveness.

A variety of rejuvenation therapies including the use of growth factors, cytokines, hormonal therapies and castration have been tested [17]. The most promising of these interventions appear to be keratinocyte growth factor (KGF), interleukin (IL)-7, and ghrelin (GRL) [17]. Although preclinical models taught us that KGF can promote thymopoiesis through enhanced survival of the thymic stromal compartment [18,19], clinical studies did not clearly confirm these findings [20,21]. Likewise, IL-7-based treatments showed increased thymic output in rodents and aged rhesus macaques, but marginal effects were observed on human thymopoiesis with preferential expansion of recent thymic emigrants and memory T cells [22-24]. Finally, the supporting role of the peptide hormone GRL in blocking thymic involution is another evolving treatment strategy for boosting T-cell output in older animals [25-29]. Unfortunately however, the effect of GRL may be limited by the gradual loss of thymic GRL receptor expression with aging [25-29]. As evidence for these therapies in stimulating thymopoiesis in higher species is yet to be clarified, the search for new compounds displaying non-redundant thymopoietic-stimulating/supporting abilities in aged subjects is needed.

Thymopoiesis relies on cytokines interplay with T-cell progenitors. In fact, prior to entering the peripheral T-cell pool, DP thymocytes must undergo restricted selection processes in the thymus via their rearranged TCR in response to self-peptides [30]. As a consequence, they become responsive to IL-7 [31]. In a quest to gain further insights into the possible role of additional cytokine(s) in supporting thymopoiesis, an *in vitro* model was developed to precisely manipulate the nature of the selecting peptide and the cytokine added to the milieu [32]. Besides the discovery of a role for IL-4 and IL-13 in positive selection and differentiation of thymocytes, the use of this high-throughput system unveiled a novel and non-redundant function for IL-21 in supporting the expansion of thymic progenitors [32]. IL-21 is the most recently identified member of the common γ-chain family of cytokines [33]. Produced mainly by activated CD4 T cells, IL-21

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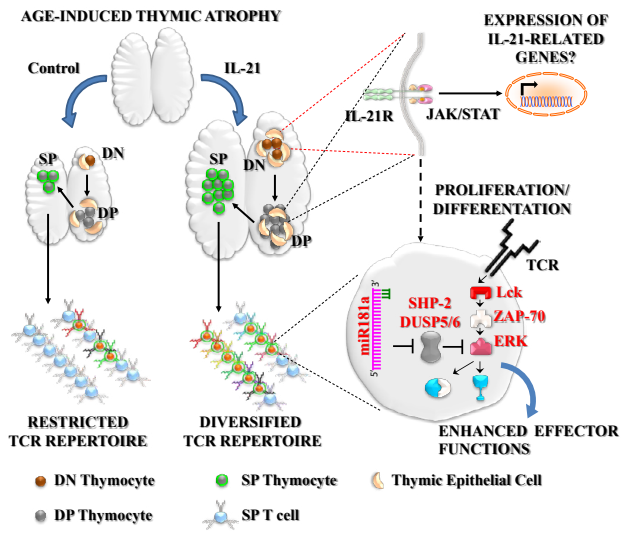

Figure 1: Schematic representation of the pharmacological effect of IL-21 in aged mice. In aging subjects, thymic function is limited leading to a restricted pool of naïve T cells. Upon IL-21 administration, enhanced proliferation of thymic progenitors is obtained via the induction of IL-21-related genes, which improves peripheral TCR diversity. In addition, newly developed naïve T cells express high amounts of miR-181a, which inhibits phosphatases targeting TCR signaling.

can: i) support CD4 T-cell differentiation down the Th17 pathway, ii) co-stimulate activated NK and CD8 lymphocytes, iii) desensitize responding cells to the inhibitory effects of regulatory T cells, and iv) act as a switch for IgG production in B cells [33,34]. Although not required for normal hematopoiesis, bone marrow progenitors expand in response to IL-21 overexpression in vivo [35]. Likewise, IL-21 did not seem to be essential for thymopoiesis due to normal T-cell development in mice deficient for the IL-21 receptor (IL-21R) [32]. However, *in vitro* peptide-mediated TCR-engagement on DP thymocytes triggered potent cell surface expression of the IL-21R leading to their expansion and enhanced generation of single-positive (SP) CD8 T cells if combined with IL-7 [32]. Based on these observations and on the fact that IL-21 can accelerate thymic recovery following pharmacologically-induced acute atrophy [36], the effect of IL-21 was evaluated for triggering *de novo* thymopoiesis in aged mice as a means to enhance their responsiveness to cancer vaccination [37]. In contrast to control aged mice, IL-21 administration was indeed capable of stimulating thymopoiesis and led to a boost in recent thymic emigrants output [37]. Accordingly, a substantial increase in the proportion of naïve T cells was observed along with noticeable improvements in TCR receptor diversity. The rejuvenated T-cell pool of IL-21-treated aged mice also exhibited lower expression levels of the TCR-inhibiting phosphatases SHP-2 and DUSP5/6 owing to augmented miR-181a expression [37] (Figure 1). The net outcome culminated in improved TCR signaling (e.g. enhanced phosphorylation of Lck, ZAP-70, and ERK) and effector functions (IL-2 secretion, CD25 expression and proliferation), which was further reflected on their enhanced anti-tumoral response to melanoma challenge following vaccination [37].

In summary, effective T-cell activation by immunotherapies or following the encountering of non-self-antigens is dependent upon two factors: a broad TCR repertoire and a pool of naïve T cells free of intrinsic defects. Unfortunately, both of these requirements are limited in aged subjects, which definitely impede the capacity of the aged immune system in generating both effective protection and a large/diverse antigen-specific T-cell memory repertoire. As reversing these deficiencies could only be achieved by stimulating thymic functions, IL-21 could be exploited as a novel immune intervention to halt and hence reverse thymic atrophy and all related immune defects associated with an aging immune system.

Disclosures

The authors declare that they have no competing financial interests.

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References

1. Jamieson BD, Douek DC, Killian S, Hultin LE, Scripture-Adams DD, et al. (1990) Generation of functional thymocytes in the human adult. Immunity 10: 569-575.
2. Zinkernagel RM, Althage A (1999) On the role of thymic epithelium vs. bone marrow-derived cells in repertoire selection of T cells. Proc Natl Acad Sci 96: 8092-8097.
3. Bhandoola A, von Boehmer H, Petrie HT, Zuniga-Pflucker JC (2007) Commitment and developmental potential of extrathymic and intrathymic T cell precursors: plenty to choose from. Immunity 26: 678-689.
4. Bhandoola A, Sambandam A (2006) From stem cell to T cell: one route or many?. Nat Rev Immunol 6: 117-126.
5. Min H, Montecino-Rodriguez E, Dorshkind K (2004) Reduction in the developmental potential of intrathymic T cell progenitors with age. J Immunol 173: 245-250.
6. Dooley J, Liston A (2012) Molecular control over thymic involution: from cytokines and microRNA to aging and adipose tissue. Eur J Immunol 42: 1073-1079.
7. Dudakov JA, Hanash AM, Jenq RR, Young LF, Ghosh A, et al. (2012) Interleukin-22 drives endogenous thymic regeneration in mice. Science 336: 91-95.
8. Goronzy JJ, Li G, Yu M, Weyand CM (2012) Signaling pathways in aged T cells - a reflection of T cell differentiation, cell senescence and host environment. Semin Immunol 24: 365-372.
9. Larbi A, Pawelec G, Wonga SC, Goldeckb D, Jing-Yi Tai J, et al. (2011) Impact of age on T cell signaling: a general defect or specific alterations? Ageing Res Rev 10: 370-378.
10. Lefebvre JS, Maue AC, Eaton SM, Lanthier PA, Tighe M, et al. (2012) The aged microenvironment contributes to the age-related functional defects of CD4 T cells in mice. Aging Cell 11: 732-740.
11. Li G, Yu M, Lee WW, Tsang M, Krishnan E, et al. (2012) Decline in miR-181a expression with age impairs T cell receptor sensitivity by increasing DUSP6 activity. Nat Med 18:1518-1524.
12. Garcia GG, Miller RA (2003) Age-related defects in CD4+ T cell activation reversed by glycoprotein endopeptidase. Eur J Immunol 33: 3464-3472.
13. Garcia GG, Berger SB, Sadighi Akha AA, Miller RA (2005) Age-associated changes in glycosylation of CD43 and CD45 on mouse CD4 T cells. Eur J Immunol 35: 622-631.
14. Tamir A, Eisenbraun MD, Garcia GG, Miller RA (2000) Age-dependent alterations in the assembly of signal transduction complexes at the site of T cell/APC interaction. J Immunol 165: 1243–1251.
15. Garcia GG, Miller RA (2001) Single-cell analyses reveal two defects in peptide-specific activation of naive T cells from aged mice. J Immunol 166: 3151–3157.
16. Garcia GG, Miller RA (2002) Age-dependent defects in TCR-triggered cytoskeletal rearrangement in CD4+ T cells. J Immunol 169: 5021-5027.
17. van den Brink MR, Alpdogan O, Boyd RL (2004) Strategies to enhance T-cell reconstitution in immunocompromised patients. Nat Rev Immunol 4: 856-867.
18. Pierce GF, Yanagihara D, Klopchin K, Danilenko DM, Hsu E, et al. (1994) Stimulation of all epithelial elements during skin regeneration by keratinocyte growth factor. J Exp Med 179: 831-840.

19. Min D, Taylor PA, Panoskaltsis-Mortari A, Chung B, Danilenko DM, et al. (2002) Protection from thymic epithelial cell injury by keratinocyte growth factor: a new approach to improve thymic and peripheral T-cell reconstitution after bone marrow transplantation. Blood 99: 4592-4600.

20. Spielberger R, Stiff P, Bensinger W, Gentile T, Weisdorf D, et al. (2004) Palifermin for oral mucositis after intensive therapy for hematologic cancers. N Engl J Med 351: 2590-2598.

21. Levine JE, Blazar BR, DeFor T, Ferrara JLM, Weisdor DJ, et al. (2008) Long-term followup of a phase I/II randomized, placebo-controlled trial of palifermin to prevent graft-versus-host disease (GVHD) after related donor allogeneic hematopoietic cell transplantation (HCT). Biol Blood Marrow Transplant 14: 1017–1021.

22. Broers AE, Posthumus-van Sluijs SJ, Spits H, van der Holt B, Löwenberg B, et al. (2003) Interleukin-7 improves T-cell recovery after experimental T-cell-depleted bone marrow transplantation in T-cell-deficient mice by strong expansion of recent thymic emigrants. Blood 102: 1534-1540.

23. Storek J, Gillespy T 3rd, Lu H, Joseph A, Dawson MA, et al. (2003) Interleukin-7 improves CD4 T-cell reconstitution after autologous CD34 cell transplantation in monkeys. Blood 101: 4209-4218.

24. Sportès C, Hakim FT, Memon SA, Zhang H, Chua KS, et al. (2008) Administration of rhIL-7 in humans increases in vivo TCR repertoire diversity by preferential expansion of naive T cell subsets. J Exp Med 205: 1701-1714.

25. Dixit VD, Yang H, Sun Y, Weeraratna AT, Youm YH, et al. (2007) Ghrelin promotes thymopoiesis during aging. J Clin Invest 117: 2778-2790.

26. van der Lely AJ, Tschöp M, Heiman ML, Ghigo E (2004) Biological, physiological, pathophysiological and pharmacological aspects of ghrelin. Endocr Rev 25: 426-457.

27. Taub DD, Murphy WJ, Longo DL (2010) Rejuvenation of the aging thymus: growth hormone-mediated and ghrelin-mediated signaling pathways. Curr Opin Pharmacol 10: 408-424.

28. Sun Y, Butte NF, Garcia JM, Smith R (2008) Characterization of adult ghrelin and ghrelin receptor knockout mice under positive and negative energy balance. Endocrinology 149: 843-850.

29. Youm YH, Yang H, Sun Y, Smith RG, Manley NR, et al. (2009) Deficient ghrelin receptor-mediated signaling compromises thymic stromal cell microenvironment by accelerating thymic adiposity. J Biol Chem 284: 7068-7077.

30. Mandl JN, Monteiro JP, Vrisekoop N, Germain RN (2013) T Cell-Positive Selection Uses Self-Ligand Binding Strength to Optimize Repertoire Recognition of Foreign Antigens. Immunity 38(2): 263-274.

31. Park JH, Adoro S, Guinter T, Erman B, Alag AS, et al. (2010) Signaling by intrathymic cytokines, not T cell antigen receptors, specifies CD8 lineage choice and promotes the differentiation of cytotoxic-lineage T cells. Nat Immunol 11: 257-264.

32. Rafei M, Rouette A, Brochu S, Vanegas JR, Perreault C (2013) Differential Effects of γc-Cytokines on Post-Selection Differentiation of CD8 Thymocytes. Blood 121: 107-117.

33. Spolski R, Leonard WJ (2008) Interleukin-21: basic biology and implications for cancer and autoimmunity. Annu Rev Immunol 26: 57-79.

34. Ozaki K, Spolski R, Feng CG, Qi CF, Cheng J, et al. (2002) A critical role for IL-21 in regulating immunoglobulin production. Science 298: 1630-1364.

35. Ozaki K, Hishiya A, Hatanaka K, Nakajima H, Wang G, et al. (2006) Overexpression of interleukin 21 induces expansion of hematopoietic progenitor cells. Int J Hematol 84: 224-230.

36. Rafei M, Dumont-Lagacé M, Rouette A, Perreault C (2013) Interleukin-21 Accelerates Thymic Recovery Ensuing Acute Atrophy. PLoS One 8: e72801.

37. Al-Chami E, Tormo A, Pasquin S, Kanjarawi R, Ziouani S, et al. (2016) Interleukin-21 administration to aged mice rejuvenates their peripheral T-cell pool by triggering de novo thymopoiesis. Aging Cell 15: 349-360.