Journal of Cell Science & Therapy
ISSN: 2157-7013

Magalhaes et al., J Cell Sci Ther 2012, 3:4
DOI: 10.4172/2157-7013.1000127

Letter Open Access

Interleukin -7 (IL-7) Increases Metabolic Thymic and CNS Activity

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Keywords: Interleukin-7; Non-Human-Primate; Immune-reconstitution; T-cells; Immunotherapy

Letter to the Editor

Interleukin-7 (IL-7) is currently used in a number of clinical trials in humans, including treatment trials for patients with HIV or HCV infection [1]. We would like to draw the attention concerning the impact of IL-7 on the central nervous system (CNS), since most clinical evaluations may not include detailed CNS examination, e.g. Positron Emission Tomography - Computed Tomography (PET-CT) or the evaluation of changes in complex behavior patterns.

IL-7, a pleiotropic cytokine, is predominantly produced by non-lymphoid cells, it protects T-cells from apoptosis and orchestrates T-cell receptor (TCR) γ rearrangement [2]. Patients with lymphopenia, either induced by chemotherapy or as consequence of hematopoietic stem cell transplantation (HSCT) show high levels of IL-7 [3,4]. IL-7 may aid to restore thymic function, it is therefore not only considered for adjunct therapy of viral infections, yet also for improved immune reconstitution after hematopoietic stem cell transplantation (HSCT). Administration of recombinant IL-7 into mice suggested that the peripheral accumulation of T cell receptor excision circles (TRECs) is *not* due to increased thymic activity, yet rather associated with the preferential accumulation of recent thymic emigrants in lymph nodes [5].

Theoretically, a broader TCR repertoire may provide TCRs capable of recognizing tumor-associated antigens, it may also aid to more effectively fight off viral infections after HSCT. Administration of recombinant IL-7 to human subjects resulted in expansion of precursor T-cells and a broadened T-cell receptor repertoire in individuals with non-hematologic cancer who received in a dose escalation study recombinant IL-7 (rIL-7), i.e. eight doses of IL-7 for eight consecutive days (60 μg/d/kg) [6] without evidence of enhanced thymic activity defined by PET-CT.

Other studies appreciated IL-7 effects on non-lymphoid tissues which suggested a broader role of this cytokine in human physiology: IL-7 is able to drive differentiation of human neuronal progenitor cells [7]. The notion that IL-7 affects the CNS was further substantiated by the demonstration that IL-7 leads to signaling in the hypothalamic arcuate nucleus (ARC) affecting hypothalamic body weight regulation along with the modulation of neuropeptides that control food intake [8]. These data warranted more detailed examination of IL-7 effects in a non-human primate (NHP) model to revisit IL-7 mediated effects on metabolic organ specific activity (Figure 1a-d).

We tested whether recombinant IL-7 (rIL-7) affects thymic and CNS metabolic activity by injecting rIL-7 into four female non-human primates (NHPs) (*Macaca mulatta*) of chinese origin, 3 years of age, body weight: 4.4 – 5.8 kg, all females (Figure 1a,b and Supplementary material S1). NHPs were injected four times, every 72 hrs with 100 μg rIL-7/kg bodyweight *s.c.* (Figure 1c). Two NHPs (females, 3 years of age, body weight: 4.4 – 5.2 kg) received only the rIL-7 diluent as a control. Immune-phenotyping of NHP peripheral blood mononuclear cells, constitutive and IL-7-induced STAT-5 phosphorylation (Supplementary Figure 1A-D), glucose, C-reactive protein (CRP), hormones adrenocorticotropic hormone [ACTH], cortisol and liver transaminases (Supplementary Table S1) were measured longitudinally. Only NHPs (4/4) who received rIL-7 showed a drop in CD4+ and CD8+ T-cells after the first rIL-7 injection (Figure 1d, Supplementary Figure S1A), yet we could not detect differences in constitutive and IL-7-induced STAT-5 phosphorylation (Supplementary Figure S1B) nor in IL-7 receptor (IL-7R) density or cell numbers in CD4+ and CD8+ T-cells (Supplementary Figure S1C). Concomitant with the drop of the absolute numbers of CD4+ and CD8+ T-cells (Supplementary Figure S1A), we observed in 2/4 animals a decreased percentage of CD4+ T cells in and an increased percentage of double negative (CD3-/+)CD4-CD8- cells in the lymphocyte compartment (Figure 1d, Supplementary Figure S1D). A F-18 fluorodeoxyglucose (FDG) FDG PET-CT was performed 24 hrs prior to the first and 8 hrs after the last (i.e. the fourth) rIL-7 injection (Figure 1c and representative raw data in Supplementary Figure S2A) and in control NHPs (average injected radioactivity: 6.36 ± 0.37 MBq/kg). The mean standard uptake values (SUV) are provided in Supplementary Figure S2B. 2/4 NHPs after rIL-7 application exhibited increased thymic glucose metabolic rates (Supplementary Figures S2A and S2B) and increased bone marrow activity, 3/4 NHPs exhibited increased CNS metabolic activity (Supplementary Figure S2B and the Supplementary Movie Files SMI5A, before and SMI5B after rIL-7 injection of animal ID 6026). We did not observe differences in liver activity before and after rIL-7 injection or differences between animals with IL-7 or saline (control) injection. Also the plasma levels of the liver enzymes alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, and C-reactive

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Received May 02, 2012; **Accepted** June 06, 2012; **Published** June 08, 2012

Citation: Magalhaes I, Sánchez-Crespo A, Pagani M, Vudattu NK, Nylen G, et al. (2012) Interleukin -7 (IL-7) Increases Metabolic Thymic and CNS Activity. J Cell Sci Ther 3:127. doi:10.4172/2157-7013.1000127

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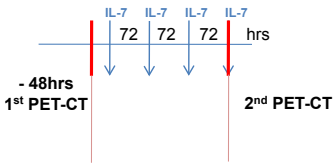
A

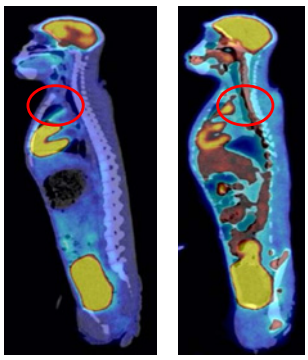


B

SUV mean	Thymus		Liver		Bone marrow		Brain	
	#	##	#	##	#	##	#	##
SMI 9046 C	**0**	**0**	**0.74**	**0.91**	**0.72**	**0.74**	**2.29**	**1.43**
SMI 6120 C	**1.08**	**1.06**	**0.88**	**0.88**	**0.77**	**0.74**	**1.9**	**2.09**
Mean	0.54	0.53	0.81	0.90	0.74	0.74	2.09	1.76
Std	*0.28*	*0.47*	*0.10*	*0.02*	*0.03*	*0*	*0.28*	*0.47*
SMI 6048	**1.82**	**1.19**	**0.76**	**0.92**	**0.6**	**0.83**	**2.22**	**1.64**
SMI 2012	**1.27**	**1.32**	**1.07**	**0.94**	**0.78**	**0.84**	**1.85**	**2.11**
SMI 6026	**1.23**	**1.62**	**0.88**	**1.11**	**1**	**0.7**	**1.8**	**3.2**
SMI 0026	**1.05**	**1.64**	**0.96**	**0.94**	**0.76**	**0.82**	**1.52**	**2.45**
Mean	1.34	1.44	0.92	0.98	0.8	0.8	1.85	2.35
Std	*0.33*	*0.22*	*0.13*	*0.09*	*0.14*	*0.06*	*0.29*	*0.66*

#1st PET-CT, ## 2nd PET-CT
#9046 C and 6120 C: control animals (no IL-7 injection)

C



D

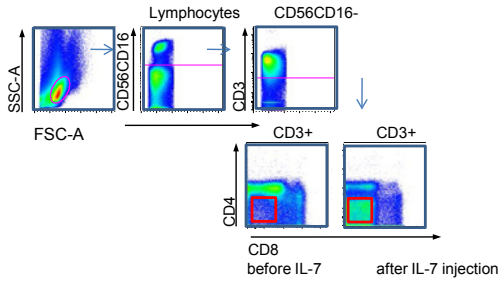


Figure 1: IL-7 increased thymic and CNS metabolic rates. A. 4 female NHPs, 3yrs old were injected with 100 µg rIL-7/kg body weight *s.c.* four times with an 72hr interval. NHPs were 3 years of age and weighted between 4.4 and 5.2 kg. 2 NHPs received only diluents as a control. A PET-CT was performed a day prior to IL-7 application and 8 hours after the last IL-7 application. **B.** Mean SUV values for the two control monkeys (SMI9046 and 6120, top panel), who received only diluents and for four NHPs who received rIL-7. Values in black are from the PCT-CT prior to IL-7 injection and values in red are derived from the PET-CT after the fourth IL-7 application. **C.** PET-CT prior to and after IL-7 application in NHP 6026, increased thymic metabolism (red circle). **D.** Loss of CD4 and CD8 cell surface expression on circulating CD3+ T-cells after IL-7 injection. Cells were gated on CD3+ T-cells, CD16+/CD56+ NK-cells were excluded, followed by staining for CD4 and CD8 T-cell markers. The red quadrant represents CD3+, CD4-, CD8- T-cells.

protein did not differ before and after rIL-7 injection, nor between animals with or without IL-7 injections (Supplementary Table S1). Similarly, ACTH (the main regulator of cortisol production), cortisol (involved on neoglucogenesis) and glucose levels did not change upon IL-7 injections (Supplementary Table S1).

The lack of FDG uptake in the study published from Sportès and co-workers [6] may most likely be linked with the older age of the study participants, the underlying malignant disease or a lack of viable thymic resources. Younger age, as in the NHPs in the current report, may be associated with viable thymic resources and subsequently increased thymic metabolism.

IL-7 injection in NHPs was shown to induce naive CD4+ and CD8+ T-cells to acquire a memory-like phenotype [9], and IL-7 injection in mice has been shown to upregulate CD8 expression [10]. Increased levels of double negative (CD3-/+)CD4-CD8- T-lymphocytes in NHPs after IL-7 treatment has not been reported up to now, the mechanism remains to be elucidated. One of the NHPs who exhibited increased thymic activity (ID 6026), showed also increased levels of CD3+/-CD4-CD8- lymphocytes after the first rIL-7 injection (Supplementary Figure S1D) which may either reflect increased thymic output of double negative CD3+CD4-CD8- T-cells or, since it coincided with a decrease frequency of CD4+ T-cells, IL-7-driven CD4+ T-cell activation leading to down-regulation of CD4 on responding T-cells.

Increased IL-7-mediated thymic activity demonstrates that viable thymic tissue can be activated in younger individuals; we observed also increased metabolic activity in bone marrow. This has also been observed in clinical studies with individuals who received 30 and 60 µg IL-7 /kg bodyweight leading to increased B-cell progenitors, yet without increased numbers of peripheral B-cells [6]. In summary, our results suggest that IL-7 is able to activate thymic tissue, if functionally receptive. Increased CNS metabolic activity after IL-7 application suggests to monitor the effects of IL-7 for more complex neurological functions and the CNS-metabolic axis in more controlled, comprehensive study settings. It also prepares to consider effects of cytokines on networks of non-lymphoid cells and tissues in patients enrolled in IL-7 trials.

Acknowledgement

The work was supported from a grant from SIDA, the Söderberg Foundation and VR, Sweden, to Markus J. Maeurer.

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