Rheumatology : Current Research
ISSN: 2161-1149

Talaber and Perl, Rheumatology 2011, 1:2
DOI: 10.4172/2161-1149.1000e103

Editorial Open Access

SLE: a Metabolic Disease of T Cells?

Gergely Talaber and Andras Perl*

Division of Rheumatology, Department of Medicine, State University of New York, Upstate Medical University, 750 East Adams Street, Syracuse, NY, 13210

SLE is a multifactorial, heterogeneous group of disease which is potentially fatal and can be characterized by anti-nuclear autoantibody production and consequent organ, especially kidney failure [1]. Therapy is still restricted and limited to general immunosuppressants and cytotoxic drugs with many side effects. Therefore, the understanding of the fine molecular mechanisms of disease pathogenesis is crucial to develop new therapeutic approaches. The complex interaction of the innate dendritic cells and adaptive immune T and B cells significantly contribute to disease pathogenesis. Both T and B cells are hyperactive in SLE. T cells exhibit aberrant signaling profile upon antigen receptor activation and changes in proximal signaling molecules and adaptor proteins which together shape the pathogenic lupus T cell phenotype.

Lupus T cells exhibit a metabolically dysregulated status, including persistent mitochondrial hyperpolarization (MHP) [2,3], increased mitochondrial mass, oxidative stress and depleted intracellular glutathione levels [4,5]. Lupus T cells also show increased cytoplasmic and mitochondrial calcium levels and signaling profile. A significant inducer of MHP is nitric oxide, which is produced mainly by monocytes in SLE. MHP leads to subsequent necrosis releasing necrotic material from T cells, which triggers dendritic cells and B cells. Closely related to MHP, T cells show altered metabolic gene expression signature, including the overexpression of the mitochondrial outer membrane protein VDAC (voltage dependent anion channel) and SOD2 (superoxide dismutase). Transaldolase, an enzyme of the pentose-phosphate pathway which is responsible for the production of nucleotides and maintenance of reducing environment [6] is also overexpressed in lupus T cells and it has been previously shown that overexpression of this enzyme results in MHP [7]. Consistent with altered metabolism, lupus T cells show enhanced activation of the mTOR (mammalian target of rapamycin) pathway [8].

mTOR is a serine threonine kinase which senses, integrates and transmits signals derived from nutrients, especially amino acids, sugars, insulin and growth factors and regulates cellular bioenergetics, cell division, protein production and autophagy [9]. mTOR is supramolecular structure which consists of mTORC1 and mTORC2. The mTOR inhibitor rapamycin and its receptor FKP12 selectively binds to mTORC1, resulting its selective inactivation, although it has been reported that continuous administration of rapamycin can inhibit mTORC2 [10]. The role of mTOR has also been implicated in non-autoimmune diseases, such as diabetes and cancer [9], but besides lupus as above, data are accumulating, that mTOR signaling play a very important role in both physiological and pathological T cell homeostasis and death.

mTOR regulates the differentiation of CD8+ memory T cells by regulating the expression of the transcription factors eomesodermin and T-bet [11]. It is important in the generation of regulatory T cells [12] in the thymus via the PI3K (phosphoinositide-3-kinase)-Akt-pathway. mTOR inhibition by rapamycin, expands Treg cells in autoimmune diabetes [13] to promote T cell immuntolerance.

Tregs, similar to other autoimmune diseases, are deficient in SLE [14] and rapamycin has been shown to be effective for improving lupus [15]. Lupus T cells isolated from rapamycin-treated patients showed decreased mTOR activity and restored T cell activation induced cytoplasmic and mitochondrial calcium-fluxing, but not MHP [15]. Furthermore, rapamycin reversed the expression of the main adaptor proteins of T cell antigen receptor pathway and calcium signaling molecules, such as the Syk kinase, the Fcε receptor, the CD3 zeta chain and Lck [8].

A recent report is about mTOR activation and downstream signaling component HIF (hypoxia-inducible factor) 1-alpha governed transcriptional regulation is required for the proper differentiation of Th17 cells suggesting that overactivation of mTOR in these cells might contribute to the development and maintenance of the autoimmunity [16]. Following activation of the HIF1α, Th17 cells exhibit more active glycolytic transcriptional program than Treg cells. As in other autoimmune diseases, Th17 cells are over-represented in lupus [17]. Significant source of IL-17 in lupus are the CD3+CD4-CD8- DN (double negative) T cells which are infiltrating the kidney. However, in SLE, not much is known about the fine-metabolic tuning of IL17-producing T cells.

Upstream of mTOR, the TSC1 (tuberous sclerosis complex) has also been intensively studied recently in genetically modified mice model and found to be an important survival mediator of not only antigen-activated, but also quiescent T cells [18]. When TSC1 was disrupted in T cells, decreased mitochondrial content and function, together with elevated level of reactive oxygen intermediates were found in these cells [19]. mTOR could also be involved in the promotion of Th1 differentiation but parallel also the inhibition of Treg differentiation via the sphingosine-1 phosphate receptor [20]. Another group identified the Rheb GTPase as an important mTORC1 component in mediating Th1-Th2 commitment [21], because Rheb-deficient T cells failed to induce Th1-Th17 mediated experimental inflammation. In the same report, selective activation of mTORC2 was related to enhanced generation of Th2, but not Th1 cells. Collectively, the mTOR kinase related signaling networks have an emerging and integrating role in mediating T helper cell lineage specification (Th1/Th2/Th17/Treg) via distinct metabolic programs [20].

Recent research in our laboratory revealed that a previously discovered human endogenous retroviral element, HRES-1, implicated in lupus pathogenesis encodes a small GTPase, HRES-1/Rab4 which co-localizes with mTOR to endosomes [8]. HRES-1/Rab4 regulates the recycling of the CD3 zeta chain and CD4 co-receptor through early endosomes and thus influences the targeting of these receptors to lysosomal degradation in T lymphocytes.

In summary, the dysregulation of cellular metabolism in lupus T cells characterized by MHP, increased mitochondrial biogenesis, oxidative stress, ATP depletion, and predisposition to necrosis,

***Corresponding author:** Dr. Andras Perl, Division of Rheumatology, Department of Medicine, State University of New York, Upstate Medical University, 750 East Adams Street, Syracuse, NY, 13210, Tel: 1 315 464 4192; Fax: 1 315 464 4176; E-mail: perla@upstate.edu

Received September 15, 2011; **Accepted** November 16, 2011; **Published** November 18, 2011

Citation: Talaber G, Perl A (2011) SLE: a Metabolic Disease of T Cells? Rheumatology 1:e103. doi:10.4172/2161-1149.1000e103

and enhanced calcium fluxing also influences the differentiation into functionally distinct subsets through the activation of mTOR. Targeting this pathway with rapamycin has shown therapeutic efficacy in SLE with the possible added benefit of extending life-span in general [22,23].

References

1. Crispín JC, Liossis SN, Kis Toth K, Lieberman LA, Kyttaris VC, et al. (2010) Pathogenesis of human systemic lupus erythematosus: recent advances. Trends Mol Med 16: 47-57.
2. Nagy G, Barcza M, Gonchoroff N, Phillips PE, Perl A (2004) Nitric oxide-dependent mitochondrial biogenesis generates Ca2+ signaling profile of lupus T cells. J Immunol 173: 3676-3683.
3. Nagy G, Koncz A, Perl A (2003) T cell activation-induced mitochondrial hyperpolarization is mediated by Ca2+- and redox-dependent production of nitric oxide. J Immunol 171: 5188-5197.
4. Gergely P Jr, Grossman C, Niland B, Puskas F, Neupane H, et al. (2002) Mitochondrial hyperpolarization and ATP depletion in patients with systemic lupus erythematosus. Arthritis Rheum 46: 175-190.
5. Gergely P Jr, Niland B, Gonchoroff N, Pullmann R Jr, Phillips PE, et al. (2002) Persistent mitochondrial hyperpolarization, increased reactive oxygen intermediate production, and cytoplasmic alkalinization characterize altered IL-10 signaling in patients with systemic lupus erythematosus. J Immunol 169: 1092-1101.
6. Perl A, Hanczko R, Telarico T, Oaks Z, Landas S (2011) Oxidative stress, inflammation and carcinogenesis are controlled through the pentose phosphate pathway by transaldolase. Trends Mol Med 17: 395-403.
7. Banki K, Hutter E, Gonchoroff NJ, Perl A (1999) Elevation of mitochondrial transmembrane potential and reactive oxygen intermediate levels are early events and occur independently from activation of caspases in Fas signaling. J Immunol 162: 1466-1479.
8. Fernandez DR, Telarico T, Bonilla E, Li Q, Banerjee S, et al. (2009) Activation of mammalian target of rapamycin controls the loss of TCRzeta in lupus T cells through HRES-1/Rab4-regulated lysosomal degradation. J Immunol 182: 2063-2073.
9. Zoncu R, Efeyan A, Sabatini DM (2011) mTOR: from growth signal integration to cancer, diabetes and ageing. Nat Rev Mol Cell Biol 12: 21-35.
10. Sarbassov DD, Ali SM, Sengupta S, Sheen JH, Hsu PP, et al. (2006) Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. Mol Cell 22: 159-168.
11. Rao RR, Li Q, Odunsi K, Shrikant PA (2010) The mTOR kinase determines effector versus memory CD8+ T cell fate by regulating the expression of transcription factors T-bet and Eomesodermin. Immunity 32: 67-78.
12. Haxhinasto S, Mathis D, Benoist C (2008) The AKT-mTOR axis regulates de novo differentiation of CD4+Foxp3+ cells. J Exp Med 205: 565-574.
13. Battaglia M, Stabilini A, Migliavacca B, Horejs-Hoeck J, Kaupper T, et al. (2006) Rapamycin promotes expansion of functional CD4+CD25+FOXP3+ regulatory T cells of both healthy subjects and type 1 diabetic patients. J Immunol 177: 8338-8347.
14. Valencia X, Yarboro C, Illei G, Lipsky PE (2007) Deficient CD4+CD25high T regulatory cell function in patients with active systemic lupus erythematosus. J Immunol 178: 2579-2588.
15. Fernandez D, Bonilla E, Mirza N, Niland B, Perl A (2006). Rapamycin reduces disease activity and normalizes T cell activation-induced calcium fluxing in patients with systemic lupus erythematosus. Arthritis Rheum 54: 2983-2988.
16. Shi LZ, Wang R, Huang G, Vogel P, Neale G, et al (2011) HIF1alpha-dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells. J Exp Med 208: 1367-1376.
17. Crispín JC, Tsokos GC (2010) Interleukin-17-producing T cells in lupus. Curr Opin Rheumatol 22: 499-503.
18. Wu Q, Liu Y, Chen C, Ikenoue T, Qiao Y et al. (2011) The tuberous sclerosis complex-mammalian target of rapamycin pathway maintains the quiescence and survival of naive T cells. J Immunol 187: 1106-1112.
19. O'Brien TF, Gorentla BK, Xie D, Srivatsan S, McLeod IX, et al. (2011) Regulation of T cell survival and mitochondrial homeostasis by TSC1. Eur J Immunol 41: 3361-3370.
20. Liu G, Yang K, Burns S, Shrestha S, Chi H (2010) The S1P(1)-mTOR axis directs the reciprocal differentiation of T(H)1 and T(reg) cells. Nat Immunol 11: 1047-1056.
21. Delgoffe GM, Pollizzi KN, Waickman AT, Heikamp E, Meyers DJ, et al. (2011) The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2. Nat Immunol 12: 295-303.
22. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, et al. (2009) Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 460: 392-395.
23. Stanfel MN, Shamieh LS, Kaeberlein M, Kennedy BK (2009) The TOR pathway comes of age. Biochim Biophys Acta 1790: 1067-1074.