Down-regulation of peroxin synthesis by silencing RNA (siRNA): A novel hypothesis for treatment of leishmaniasis

Sir,

Kinetoplastida such as genera *Leishmania* and *Trypanosoma* are characterized by a number of unique features with respect to their energy and carbohydrate metabolism. Several metabolic and biochemical differences have been identified between host and parasite that can be exploited as drug targets in the development of new antileishmanial agents. Some of their metabolic pathways including sterol biosynthesis, glycolytic pathway, purine salvage pathway, glycosylphosphatidylinositol biosynthesis, protein kinases, proteinases, folate biosynthesis, glyoxalase system, trypanothione pathway, topoisomerase pathway and hypusine pathway are potential drug targets in *Leishmania*.

These organisms possess peculiar peroxisomes called glycosomes, membrane-enclosed organelles that contain glycolytic enzymes, which play a central role in their metabolism. Glycosomes are organelles found only in the kinetoplastid protozoa and regularize several important catabolic and anabolic pathways, including the first six steps of glycolysis, the pentose phosphate pathway, purine salvage and pyrimidine biosynthesis.[1] Glycosomal compartmentalization has been hypothesized to be required for the high glycolytic rate of African trypanosomes.[2] The glycosome is also thought to be the site of synthesis of ether-linked lipids which in *Leishmania* comprise the plasma membrane anchor of a major surface virulence determinant, the lipophosphoglycan.[1,2] The compartmentalization of these critical metabolic pathways has led to the consideration of the glycosome as a potential target for drug development. It seems likely that inhibiting the import of glycosomal proteins would prove deleterious to the parasite.

One of the validated drug targets is the glycolytic pathway which is important in the *Leishmania* life cycle.[3] The Krebs cycle does not occur in *Trypanosoma* and *Leishmania* ¸ and they use glycolysis as their exclusive mode of adenosine triphosphate (ATP) generation. If the biochemical processes within the glycosome are stopped or new organelles not formed, the resulting loss of its only source of energy (glycolysis) would be life-threatening to the parasite. Therefore, preventing the assembly of new glycosomes may be key to limiting the growth of the parasite. Glycosome assembly needs glycosomal proteins and lipids and occurs by a combination of vesicles derived from the endoplasmic reticulum. These proteins are synthesized by free ribosomes in the cytoplasm and then joined to the glycosome structure. Many of these proteins are enzymes essential for parasite cell survival. Glycosome assembly also requires a class of proteins called peroxins. Peroxin 5 and peroxin 7 are the cytosolic receptors for other glycosomal proteins which bind and move them into the organelles. If synthesis of these two important proteins is blocked, glycosome assembly does not occur and the parasite cannot survive. Inhibition of the synthesis of peroxins 5 and 7 could therefore be considered as a novel therapeutic strategy.[4,5]

Methods to prevent protein synthesis in eukaryotic organisms such as *Leishmania* may inhibit the synthesis of proteins in human cells as well and cause clinical complications. In recent years, RNA interference has been used to inhibit gene expression by degradation of target messenger RNA (mRNA) using silencing RNA (siRNA) in a variety of protozoan parasites such as *Leishmania* spp.[6,7] In this method, a double strand of siRNA sequences (20–25 base pairs) is synthesized complementary to the target mRNA. Single-stranded siRNA in the cytosol pairs with its complementary sequence on the target messenger RNA (mRNA), triggering its cleavage and thereby inhibiting protein synthesis.[8] Considering the importance of peroxins 5 and 7 to *Leishmania*, siRNA complementary to their mRNA can be designed which could decrease the expression of these peroxins leading to the death of *Leishmania* as an intracellular parasite.

It thus seems possible to design compounds to prevent interactions of proteins involved in the biogenesis of *Leishmania* glycosomes without interfering with peroxisome formation in human host cells. Such compounds would be suitable as lead drugs against leishmaniasis. Our hypothesis offers this potential therapeutic target for *in vitro* experiments.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Masoud Keighobadi, Saeed Emami[1], Abbas Khonakdar Tarsi[2], Mahdi Fakhar[3]

Student Research Committee, Faculty of Pharmacy, Mazandaran University of Medical Sciences, [1]Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, [2]Department of Biochemistry, Biophysics, and Genetic, School of Medicine, Mazandaran University of Medical Sciences, [3]Molecular and Cell Biology Research Center, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

Address for correspondence: Dr. Mahdi Fakhar, Molecular and Cell Biology Research Center, School of Medicine, Mazandaran University of Medical Sciences, Farah-Abad Road, P.O. Box: 48175-1665, Sari, Iran.
E-mail: mahdif53@yahoo.com

REFERENCES

1. Opperdoes FR, Michels PA. The glycosomes of the *Kinetoplastida*. Biochimie 1993;75:231-4.
2. Turco SJ. Surface constituents of *Kinetoplastida* parasites. In: J. Joseph Marr and Miklós Müller, Biochemistry and Molecular Biology of Parasites. San Diego, California: Academic Press; 1995. p. 177-202.
3. Dumas C, Ouellette M, Tovar J, Cunningham ML, Fairlamb AH, Tamar S, *et al.* Disruption of the trypanothione reductase gene of *Leishmania* decreases its ability to survive oxidative stress in macrophages. EMBO J 1997;16:2590-8.
4. Rybicka KK. Glycosomes – The organelles of glycogen metabolism. Tissue Cell 1996;28:253-65.
5. Parsons M. Glycosomes: Parasites and the divergence of peroxisomal purpose. Mol Microbiol 2004;53:717-24.
6. Kolev NG, Tschudi C, Ullu E. RNA interference in protozoan parasites: Achievements and challenges. Eukaryot Cell 2011;10:1156-63.
7. Bhattacharyya S, Dey R, Majumder N, Bhattacharjee S, Majumdar S. A novel approach to regulate experimental visceral leishmaniasis in murine macrophages using CCR5 siRNA. Scand J Immunol 2008;67:345-53.
8. Rao DD, Vorhies JS, Senzer N, Nemunaitis J. siRNA vs. shRNA: Similarities and differences. Adv Drug Deliv Rev 2009;61:746-59.

Access this article online	
Quick Response Code:	Website: www.ijdvl.com
	DOI: 10.4103/0378-6323.181473

How to cite this article: Keighobadi M, Emami S, Tarsi AK, Fakhar M. Down-regulation of peroxin synthesis by silencing RNA (siRNA): A novel hypothesis for treatment of leishmaniasis. Indian J Dermatol Venereol Leprol 2016;82:436-7.

Received: December, 2014. **Accepted:** January, 2016.