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.

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