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Minireview

Unraveling the components of protein translocation pathway in human malaria parasite *Plasmodium falciparum*

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Abstract

The targeting and translocation of proteins is an essentially required and conserved process in all the living organisms. This complex process involves multiple steps and requires a variety of factors before the protein reaches its final destination. The major components of translocation machinery are signal recognition particle (SRP) and secretory (Sec) complex. These are composed of highly conserved components. SRP contains SRP RNA and other polypeptides such as SRP9, SRP14, SRP19 and SRP54. Sec complex is composed of Sec61αβγ, Sec62 and Sec63. In this review using bioinformatics approach we have shown that the *P. falciparum* genome contains the homologues for all of these and other factors such as SRP receptor, and TRAM (translocation associated membrane protein), which are required for post- and co-translational protein translocation. We have also shown the various steps of translocation in a hypothetical model.

Keywords: Biological membrane; Malaria parasite; Protein translocation; Ribosome; Signal peptide; Signal recognition particle

The translocation of proteins across or inside the membranes is a fundamental process in all the different living organisms such as bacteria, humans, archaea, plants and all the rest of the kingdoms of life [1]. This is an essential requirement because proteins functioning in diverse locations nevertheless are synthesized mainly in the cytosol. The transport of proteins is performed by a complex structure in the endoplasmic reticulum membrane consisting of several proteins. The proteins intended for secretion contain the amino-terminal extensions known as signal peptides and are directed into these pathways. Signal peptidases (SPases)[1] are responsible for proteolytically cleaving the signal peptides from the precursor during or shortly after translocation [2]. Signal recognition particle (SRP) is ubiquitous and one of the very few functional small ribonucleoprotein particles, which has increased in complexity during evolution. The composition of SRP varies extensively and it is an essential multi-protein–RNA complex. SRP binds the ribosomes and is responsible for the co-translational targeting of the signal peptide containing proteins to the biological membranes such as plasma membrane in prokaryotes and the endoplasmic reticulum membrane in eukaryotes. First by recognizing the nascent signal sequence followed by the recognition of the SRP receptor in the membrane, SRP directs the protein en route to the proper cellular compartment [3]. The signal sequence recognition is associated with a transient retardation of protein synthesis, which is known as elongation arrest [4]. It has been suggested that this activity pauses translation during targeting, so that the ribosome nascent chain (RNC) is capable to interact with the translocation channel that is also called translocon [4]. RNC and SRP complex is formed when the SRP binds to the signal peptide, which emerges from the exit side of the ribosome. This complex then docks with a membrane anchored SRP receptor in a

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[1] *Abbreviations used:* Bip, binding protein; ER, endoplasmic reticulum; Hsp, heat shock protein; PCC, protein conducting channel; RNC, ribosome nascent chain; Sec, secretory; SRPR, SRP receptor; SRP, signal recognition particle; TRAM, translocation associated membrane protein.

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GTP-dependent manner and as a result the protein is translocated across or integrated into the membrane through the translocon [5]. Subsequent binding of SRP leads to a pause in peptide elongation and the process of translation continues after the dissociation of SRP from this complex. SRP receptor (SRPR) is a membrane protein containing two subunits, SRPRα and SRPRβ, each of which also harbors a GTP-binding domain. SRPR binding to SRP causes the latter to dissociate from both the ribosome and the signal sequence in the presence of GTP. Subsequently GTP hydrolysis leads to the release of SRP from the SRPR, which is then returned to the cytosol [6].

Table 1
Components of protein translocation pathway in *P. falciparum*

S. No.	Gene name	PlasmoDB No.	Size (protein kDa)	Introns	% Homology with humans
1.	SRP 9	MAL7P1.158	12.8	4	31
2.	SRP 14	PFL0160w	11.8	1	37
3.	SRP 19	PFL0785c	18	0	33
4.	SRP 54	PF14_0477	55.9	0	50
5.	SRPR α	PF13_0350	65.1	0	35
6.	SRPR β	PFL2245w	30.6	3	26
7.	TRAM	PF14_0034	40.4	0	31
8.	Sec 61α	MAL13P1.231	50.9	0	67
9.	Sec 61β	MAL8P1.51	11.2	3	45
10.	Sec 61 γ	PFB0450w	9.2	0	59
11.	Sec 62	PF14_0361	39	0	23
12.	Sec 63	PF13_0102	75.8	0	27

Plasmodium falciparum is a protozoan parasite, which causes malaria and thus has a major impact on human health [7,8]. This parasite multiplies in two hosts mosquito and human and during the development in human liver and red blood cells it secrets and targets the proteins to various compartments. The genome of this parasite has been completely sequenced and since 2002 the malaria research has entered the post-genomic era [9]. The *P. falciparum* genome contains 14 chromosomes which encode ~5400 genes, a linear mitochondrial genome and a circular plastid-like genome [10]. Although it has been reported that the parasite genome contains homologues for a number of genes but due to the A – T richness of the genome a number of gene

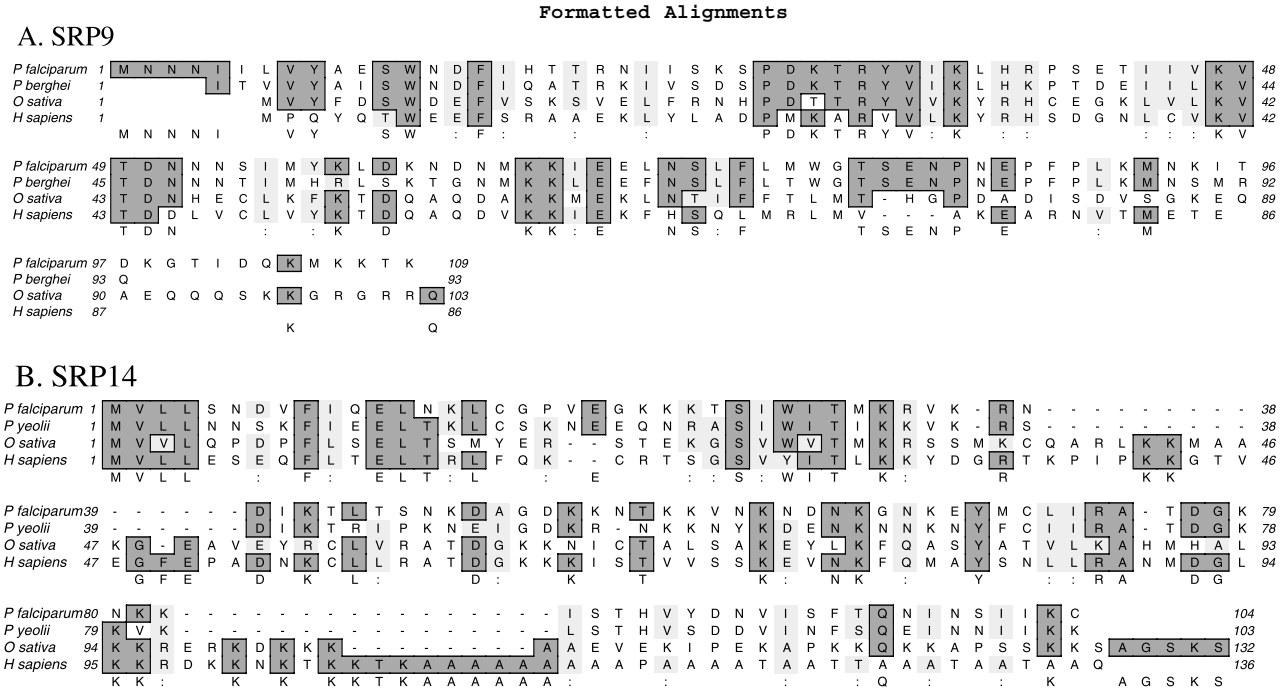

Fig. 1. (A) Comparison of amino acid sequences of *P. falciparum* SRP9 (PlasmoDB No. MAL7P1.158) with SRP9 from *Plasmodium berghei* (XP_677698), *Oryza sativa* (BAD46311) and *Homo sapiens* (NP_003124). The accession numbers of the aligned sequences are written in brackets. (B) Comparison of amino acid sequences of *P. falciparum* SRP14 (PlasmoDB No. PFL0160w) with SRP14 from *Plasmodium yoelii* (XP_725721), *Oryza sativa* (CAA71204) and *Homo sapiens* (NP_003125). The accession numbers of the aligned sequences are written in brackets.

Fig. 2. (A) Comparison of amino acid sequences of *P. falciparum* SRP19 (PlasmoDB No. PFL0785c) with SRP19 from *Plasmodium berghei* (XP_676627), *Oryza sativa* (NP_001057570) and *Homo sapiens* (NP_003126). The accession numbers of the aligned sequences are written in brackets. (B) Comparison of amino acid sequences of *P. falciparum* SRP54 (PlasmoDB No. PF14_0477) with other SRP54 from *Plasmodium berghei* (XP_678308), *Oryza sativa* (NP_001044395) and *Homo sapiens* (P61011). The accession numbers of the aligned sequences are written in brackets. (C) Computer based structural modeling of PfSRP54. Computer-predicted structures of SRP54 from (i) *Homo sapiens* and (ii) *P. falciparum* and (iii) Super-imposed structure of the two models. The complete protein sequences of SRP54 from *P. falciparum* and *H. sapiens* were submitted to the JIGsaw program (http://www.bmm.icnet.uk/servers/3djigsaw/). Three-dimensional models based on the published crystal structure for these were created using the molecular visualization program and the VMD software (www.ks.uiuc.edu).