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Transcript maturation in apicomplexan parasites

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The complex life cycles of apicomplexan parasites are associated with dynamic changes of protein repertoire. In *Toxoplasma gondii*, global analysis of gene expression demonstrates that dynamic changes in mRNA levels unfold in a serial cascade during asexual replication and up to 50% of encoded genes are unequally expressed in development. Recent studies indicate transcription and mRNA processing have important roles in fulfilling the 'just-in-time' delivery of proteins to parasite growth and development. The prominence of post-transcriptional mechanisms in the Apicomplexa was demonstrated by mechanistic studies of the critical RNA-binding proteins and regulatory kinases. However, it is still early in our understanding of how transcription and post-transcriptional mechanisms are balanced to produce adequate numbers of specialized forms that is required to complete the parasite life cycle.

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Introduction

Unicellular eukaryotic parasites of the Apicomplexa phylum have complex lifestyles that involve propagation in different hosts accompanied by major morphological transformations needed to move between hosts. Parasite survival greatly depends on changes of gene expression and in *Toxoplasma* ~2–5% of encoded genes are thought to be uniquely expressed in each developmental stage [1,2]. A remarkable serial order of gene expression is also associated with parasite replication with nearly 40% of mRNAs cyclically expressed that is thought to deliver proteins in a 'just-in-time' sequence to daughter parasites [3,4]. The profiles of cyclical mRNAs are particularly dramatic in the S and mitotic periods (including cytokinesis) of the parasite cell cycle when many specialized structures and invasion organelles are produced *de novo*.

Our understanding of how gene expression in the Apicomplexa is regulated has significantly improved in recent years. In parasite development there is a clear evidence of classical mechanisms based on *cis–trans* regulation of a core promoter complex, which involves the activity of large families of plant-related AP2 transcription factors [4,5,6•,7,8•] and chromatin remodelers [9,10•]. By contrast, the mechanisms responsible for cell cycle mRNA profiles in the asexual stages is less understood and here the role of ApiAP2 factors is much less clear. Nearly 75% of ApiAP2 factors with peak expression in the S/M periods of the *Toxoplasma* tachyzoite cell division are dispensable (White and Hong, unpublished results) and some late cell cycle ApiAP2 factors have exclusive roles in development [8•]. A partial answer to this paradox may lie downstream of transcriptional initiation. There are extensive RNA-based machineries in these parasites responsible for transcript maturation (splicing, mRNA capping and polyadenylation) and mRNA stabilization (protection, degradation) that may act in accord with translational control (RNP granules, μORFs, and mi-RNAs) in order to coordinate cell cycle gene expression profiles. There are excellent reviews of Apicomplexa translation control [11••], therefore, here we will focus on nuclear mRNA processing with emphasis on the splicing machineries and their regulation.

Whole cell mRNA analysis

Recent deep RNA sequencing has confirmed the extensive cell cycle mRNA cascade that unfolds in these parasites [12••,13,14,15••] and has also provided a more complete view of the RNA landscape that has aided gene annotation, identified alternative splice sites, and precisely mapped 3′ and 5′ UTR ends [15••,16,17]. New groups of RNA were identified by these efforts including long non-coding, anti-sense RNA [12••,15••,18••,19] and a wealth of the small RNAs [15••,20•]. These last discoveries are not yet understood given that parts of the RISC machinery are absent from Apicomplexa genomes [20•,21].

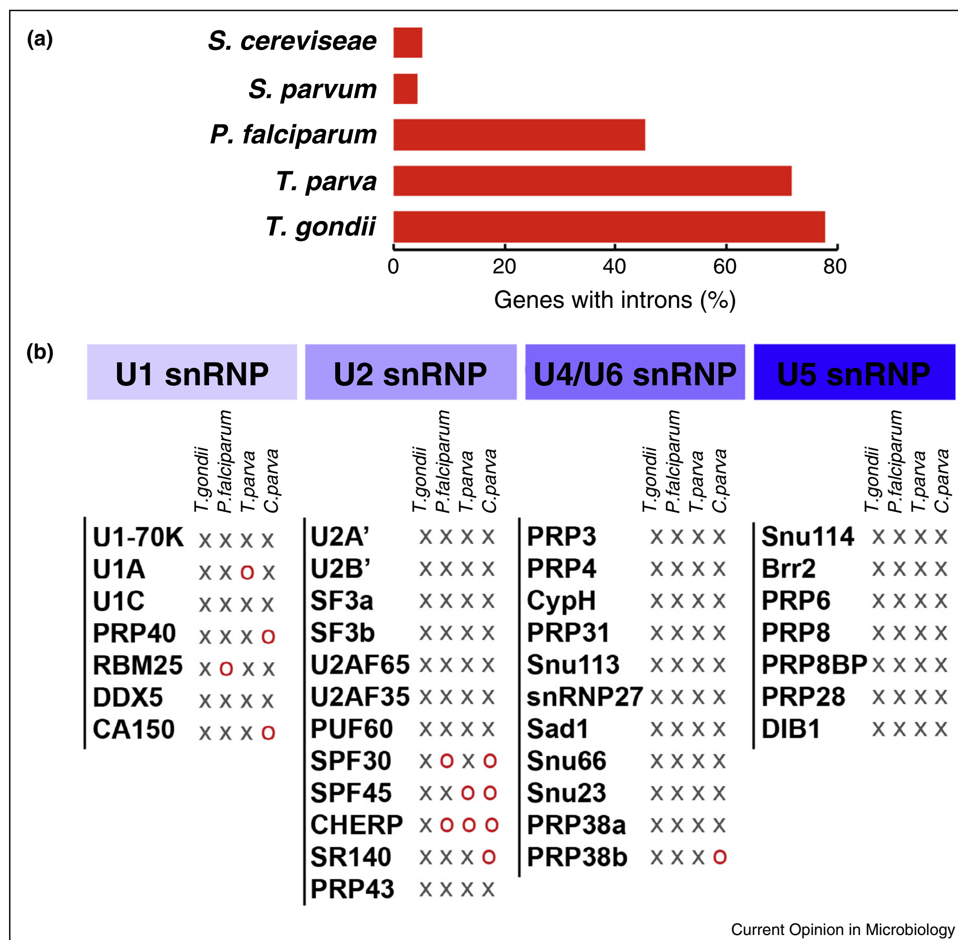
Overall RNA sequencing has discovered ~20% more transcripts [12••,15••,16] with ~5% of genes in *Plasmodium falciparum* producing an average 2–4 or more transcripts [15••]. Different types of alternatively spliced (AS) mRNAs were detected with alternative donor and acceptor types being predominant and transcript truncation the largest fraction of AS-transcripts in *P. falciparum* [12••,15••]. These findings explain the presence of

nonsense-mediated mRNA decay (NMD) machinery in Apicomplexa genomes [15••,18••], which is widely used by other eukaryotes to regulate protein abundance. Importantly, these results indicate that the Apicomplexa produce futile RNAs that are likely regulated by NMD process. Whole-genome assessment of AS-transcripts has also revealed unexpected linkage between different levels of gene regulation. For example, AS-forms of *P. falciparum* PF3D7_0103200 and PF3D7_0601200 mRNAs associate exclusively with loaded ribosomes [18••], denoting selective use of the alternative transcripts at the certain stage of the parasite life. To understand how widespread these mechanisms are we will need to characterize the translated transcriptome in each parasite.

Major splicing machinery in Apicomplexa

Assembled genomes of Apicomplexa species reveal different gene organization with introns present in 5% of genes in *Cryptosporidium* as compared to >75% of genes in *Toxoplasma* (Figure 1a). Intron sequences in *P. falciparum* [15••,22••] and *Toxoplasma* [23–25] have the canonical 5′ GU-AG 3′ splice junction, and because of the AT-rich genome, *P. falciparum* has uniquely replaced the canonical G in the 5th position of the 5′ splice site with no apparent reduction in splicing efficiency [22••,26]. Apicomplexa introns have significant nucleotide variations at the branch point and there is an indication of additional regulatory elements located in introns and exons [22••]. RNA-binding proteins of heterogeneous ribonucleoprotein (hnRNP) and serine/arginine-rich (SR) family are widely used in other eukaryotes to modulate the splice site recognition via binding to enhancer or silencer sequences [27,28] and many of these factors are encoded in Apicomplexa genomes (Table S1) [29••]. In model eukaryotes these splicing regulatory elements are known to contribute significantly to the splicing

Figure 1



Spliceosome machinery in Apicomplexa phylum. **(a)** Percentage of the genes with introns was determined in four model apicomplexans (*Toxoplasma gondii*, *Plasmodium falciparum*, *Thieleria parva*, *Cryptosporidium parvum*) and compared to the relatively low-intron content of yeast (*Saccharomyces cereviseae*). **(b)** Spliceosome components present in Apicomplexa genomes; major U1, U2, U4/U6 and U5 snRNP complexes were analyzed. Orthologs of human splicing factors were identified by pBLAST and gene IDs and e-values are listed in Supplemental Information (Table S1). Existing orthologs are indicated with an X, absent components are indicated with an O.

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