Review Article

Trypanosoma Variant Surface Glycoprotein: A Review

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Abstract

The glycoprotein surface of the *Trypanosoma* parasite plays a crucial role in the organism's biology, as a protective barrier that facility invasion to the host. The special structures of these glycoproteins contribute to the *Trypanosoma* ability to evade the host. This provides a crucial role of the pathogenesis of this parasite by enabling *Trypanosoma brucei* to escape from the immune responses by variant its surface glycoprotein (VSG). Hence, *T. brucei* can keep persistence in the bloodstream. Making it a main factor in the pathogenesis of sleeping sickness disease. Furthermore, understanding the VSG functions would offer valued aspects to beneficial targets for medication caused by *Trypanosoma* species. As well as it elucidates the mechanisms for vaccine development and cell signaling strategies. By understanding of VSG, jobs improve the awareness of parasite biology to reduce the burden of *Trypanosoma* species infections and fast-track development of both effective targeting drugs and supportive vaccines in the scientific community. This collaboration between researchers can be translated into practical explanations to mitigate these diseases towards the eradication of African trypanosomiasis on public health.

Keywords: African sleeping sickness, *Trypanosoma brucei*, variant surface glycoprotein, VSG

Introduction

The study of parasitic organisms offers critical insights into complex biological mechanisms, particularly in the context of host-pathogen interactions. Amongst these organisms, *Trypanosoma brucei*, the causative agent of African sleeping sickness, has garnered significant attention due to its remarkable ability to evade the host immune response(1).Central to this phenomenon is the variant surface glycoprotein (VSG), a key component in the parasite's antigenic variation strategy(2). This ability to continuously alter its surface proteins allows *T. brucei* to persist within the host, complicating treatment and prevention efforts. A thorough examination of VSG reveals its intricate structure and function, which are essential in mediating immune evasion(3). The genetic diversity inherent in the VSG gene family facilitates the production of a vast repertoire of glycoproteins, each capable of triggering different immune responses(1,4). This dynamic characteristic not only aids in the parasite's survival but also highlights the adaptive nature of pathogens in response to host defences(4).Understanding the molecular biology of VSG provides essential implications for developing effective therapeutic strategies against *Trypanosoma* infections. By studying the mechanism and genes behind trypanosomes VSG expression and variation, researchers can identify potential targets for disentangling the genetic code of the parasite(5).This review underpins the broader importance of exploring *Trypanosomes* VSG that challenge humans' and animals' health, emphasizing on the need for innovative approaches to combat persistent evading of the host immune system.

Significance of *Trypanosoma* in Public and Veterinary Health

The genus *Trypanosoma* encompasses several parasitic species that significantly impact both human and animal health, contributing to a complex interplay between the parasites and their hosts. Notably, *T. brucei*, responsible for human African trypanosomiasis, has evolved sophisticated immune evasion strategies, such as antigenic variation, allowing it to persist in the bloodstream and evade host defences(6). This ability to manipulate host immune responses complicates vaccine development and poses challenges for effective treatments. In

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addition to its impact on human health, *Trypanosoma* affects livestock, leading to substantial economic losses(7). The heavy toll on both human and animal populations underscores the importance of understanding the molecular mechanisms behind trypanosome survival, including the role of variant surface glycoproteins (VSG) in immune evasion and pathogenesis(8). Consequently, lessening the effects of *Trypanosoma* is critical for enhancing health outcomes and nourishing life in affected regions(9).

VSG Switching as a Strategy for *Trypanosoma bruci* Survival

In the course of an infection, the parasite exhibits antigenic variation by 'switching' the expression of the VSG, drawing from a genomic repertoire that includes over 1000 VSG-encoding genes (10). In *T. b. brucei*, approximately 80% of this repertoire is made up of incomplete genes or pseudogenes(7). An mRNA from a VSG is generated through transcription at one of approximately 15 telomeric bloodstream expression sites, whereas the remaining bloodstream expression sites stay transcriptionally inactive. Therefore, only a single VSG is found on the surface of the parasite, unless the parasite is in the process of VSG switching(11,12). Transcription may be turned off at certain bloodstream expression sites while being turned on at others to modify the expressed VSG (*in situ* switching), or new VSG genes can be inserted into bloodstream expression sites through gene conversion. VSG switching can take place through telomere exchange, which involves the recombination of VSGs between two bloodstream expression sites(13). The architecture of VSGs is essential for the function and survival of *T. brucei* and is distinguished by their abundant presence on the surface of parasites, forming the primary component of the outer coat of trypanosomes(8). This compact arrangement obstructs the identification and attachment of host antibodies, enabling certain subpopulations of the parasite to endure even under immune pressure. The biosynthetic processes that regulate VSG production are intricate, featuring a distinctive mechanism of allelic exclusion that ensures only one VSG gene is expressed at any given moment, positioned near the telomeres(14). This facilitates quick transitions amongst VSG variants, adding complexity to the host's immune response. Grasping the complex aspects of VSG structure and function is essential for formulating therapeutic approaches to combat trypanosomiasis, as it emphasises the parasite's adaptive abilities and points out possible intervention targets(15).

The Role of VSG in Immune Evasion

The variant surface glycoprotein (VSG) of *T. brucei* plays a pivotal role in immune evasion, largely due to its remarkable molecular characteristics. Each trypanosome expresses a singular VSG, which forms a dense protective coat that shields the parasite from host antibodies(5,16). This antigenic variation is facilitated by the extensive genomic repertoire of VSG genes, allowing the parasite to repeatedly alter its surface antigens(8). In addition, studies have shown that the dynamics of VSG coat replacement are crucial; for instance, the complete replacement process requires several days, during which the parasite is briefly susceptible to early responding immunoglobulin M antibodies(12,17). Moreover, specific biochemical features of VSGs, such as unique glycan modifications, enhance virulence and promote evasion of host immunity, exemplifying the sophisticated strategies employed by *T. brucei* to survive within the host(14). Hence, the intricacies of VSG molecular characteristics significantly contribute to the parasites ability to persist despite ongoing immune challenges(4).

Molecular Variation and Antigenic Diversity

The intricate mechanisms underlying genetic variation in *T. brucei* are pivotal for the pathogens survival and its ability to evade the host immune response(3). Such parasitic surface variation is employed by altering their Glycoproteins (VSGs) in their surface to hide from host's adaptive immunity(6,15). A critical examination of comparative genomic data reveals that while *Trypanosoma Congolese* utilises variants from multiple ancestral VSG lineages, *T. brucei* displays more recent VSG origins with a remarkable ability to co-opt ancestral genes for new functions(11,18). In addition, the molecular pathways governing VSG recombination highlight species-specific differences, particularly in the frequency and mechanism of genetic exchanges, reinforcing the importance of genetic diversity in sustaining chronic infections(19). Understanding these evolutionary dynamics not only sheds light on the survival strategies of these parasites but also informs potential interventions to combat African trypanosomiasis(20).

Machinery of VSG Gene Expression Disease Occurrence

The VSG gene expression in *T. brucei* is composed by a complex regulatory system that enables the parasite to evade the host immune response, by facilitating disease persistence(14). Mechanisms such as antigenic variation allow the trypanosome to switch their VSG protein displayed on its surface(21). This continuous alteration of surface antigens not only confounds the host antibody production but also hinders effective memory cells, as the host immune response repeats adaptation to new antigenic structures. In addition, trypanosomes actively suppress B-cell responses, impairing the overall humoral immunity of the infected host(22). This combination is contributing significantly to the chronic nature of trypanosomiasis, resulted to health implications of populations and complicating the development of effective vaccines(5).

Although the unique patterns of parasitemia linked to *Trypanosoma* caused by *T. brucei* were first observed over a 100 years ago, the precise dynamics of the interaction between VSG and the humoral immune response are still under investigation(22). VSG switching is described as 'semi-predictable', with certain VSGs recognised for their

earlier emergence during infection in comparison to others(14). This is linked to the genomic position of VSG proteins which are detected early in the contagion development due to their similar homologous sequence. Altering rate of VSG expression in *Trypanosoma* plays an important role in the infection dynamics by allowing rapid evasion of the host immune system(23). A recent finding denies this rate of substituting VSG just happened for the evasion through infection, and the estimated trypanosome can express more than 100 VSGs. This diversity may compensation for the steady of VSG variants. A new variant named 'mosaic' VSGs can arise from gene sequences of VSG that probably yield a diversity of non-functional nor cross-reactively of VSGs(11). This mosaic variant is expected to overcome the latent of contamination stages due to its various displays of VSG expression and it's important for maintaining the chronic infection lasting for months or years(24). As a result, when this complete genomic repertoire of mosaic VSGs is exhausted *in vivo* presses, and the parasite must produce new variants. The rate of altering of VSG proteins in African trypanosomes was measured, in previous *in vivo* studies, indicating that the altering rate getting to 10–3 changes per population(11). While *in vitro* studies observed a significant low change rate(25). This is possibly due to the different strains of trypanosome used in each trial. Besides, this rate of switching probably differs according to confident environmental factors, a study stated that the switching rate in the same parasite strain rises by increasing fly transmission(2,10). Antigenic variation of *T. brucei* strain has been implied in mouse models by using resulted in different natural infections including minimum the parasite movement of crosswise the tissue regardless the rate of swapping frequency of the parasitemia waves experiential noticed during infection(26).

Significant boosts in expression level, growth into a huge paralogous gene ancestor and the introduction of monoallelic expression were all necessary to create the VSG system, although the sequence of events is unclear [Figure 1]. Exploring associated genomes reveals how VSG has developed, with major proof of continuing and lineage-specific diversification within this family(27). For example, *Trypanosoma vivax* VSG is more diverse than *T. brucei* with evidence of asymmetrical recombination occurrences between taxa and low convergence between the repertoires. A profound divide into two separate subfamilies, VSG-a and VSG-b, appears to have persisted throughout the evolution of the African lineage, indicating the separation between these two subfamilies developed earlier(26).

Conclusion

The ability of *T. brucei* to continuously alter its VSG coat facilitates persistent infection and hinders antibody-mediated clearance, as demonstrated by the dynamics of VSG coat replacement during host interactions. Therefore, the identification of critical VSG structure and expression in immune evasion mechanisms emphasises the necessity for targeted therapeutic strategies that disrupt VSG functionality or impede flagellar motility, as observed in previous studies. Eventually, advanced studies of the molecular machinery behind VSG expression could pave the way for innovative treatments for trypanosomiasis and inform broader approaches

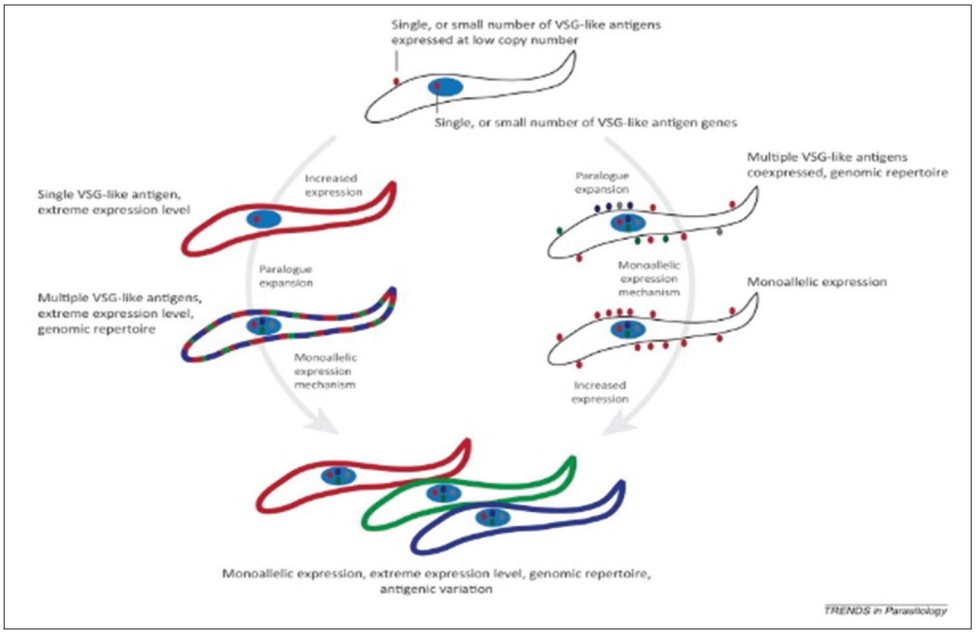

Figure 1: Illustration of steps of immunity evasion machinery in *Trypanosoma brucei*. The model on the right depicts the paralogous development of the proto-VSG prior to the establishment of a monoallelic expression system and the emergence of high expression levels. According to the model on the left, paralogous expansion occurred when high levels of expression first developed, resulting in the formation of a complex, thick coat that included several proto-VSGs. The condition observed in African trypanosomes was then brought about by the addition of a monoallelic expression mechanism. Illustration taken from a study by Manna *et al*.(27)

to combat similar host-pathogen interactions in other infectious diseases.

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Conflicts of interest

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