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Schistosoma mansoni egg glycoproteins and C-type lectins of host immune cells: Molecular partners that shape immune responses

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ABSTRACT

Schistosome eggs and egg-derived molecules are potent immunomodulatory agents. There is increasing evidence that the interplay between egg glycoproteins and host C-type lectins plays an important role in shaping immune responses during schistosomiasis. As most experiments in this field so far have been performed using complex protein/glycoprotein mixtures or synthetic model glycoconjugates, it is still largely unclear which individual moieties of schistosome eggs are immunologically active. In this review we will discuss molecular aspects of *Schistosoma mansoni* egg glycoproteins, their interactions with C-type lectins, and the relevance to schistosome egg immunobiology.

1. Introduction

In schistosomiasis, parasite eggs play an essential role in shaping immune responses (Pearce and MacDonald, 2002). In the case of *Schistosoma mansoni*, each adult worm pair releases 200–300 eggs in the mesenteric veins each day in an immature form consisting of an egg shell of cross-linked proteins containing an ovum and vitelline cells. While still in the host, the egg matures during 5–6 days by the development of the ovum to a miracidium, and the formation of the Von Lichtenberg's envelope on the inside of the egg shell from which proteins are secreted into the environment through pores (Fig. 1) (Neill et al., 1988; Ashton et al., 2001). Many of the eggs traverse the gut tissue and are excreted with the feces, but a significant number get lodged downstream in the liver where they eventually die.

The host reacts to eggs and egg products by inducing a Th2-mediated immune response which may lead to granulomatous inflammation and pathological tissue remodeling and fibrosis (Pearce, 2005). It is not clear if particular egg components are critical for the extravasation of the eggs from the blood vessels. Since freshly laid immature eggs are not yet believed to secrete proteins (Neill et al., 1988; Ashton et al., 2001), one could hypothesize that the egg shell is involved in this process. More clearly however, the eggs' secretory proteins (ES) which are formed in the sub-shell area upon maturation and secreted into the egg's environment (Ashton et al., 2001), induce a major immune response of the host that appears to be leading to Th2 polarization. To other components of the egg, such as the hatching fluid and most of the so-called soluble egg antigens (SEA), the host will most likely be exposed only when eggs die and fall apart in host tissues.

While a number of recent studies have identified single components of ES and SEA with immunomodulatory properties (Asahi et al., 1999; Schramm et al., 2003; Donnelly et al., 2008; Everts et al., 2009; Steinfelder et al., 2009), the vast majority of all molecular studies into the immune mechanisms induced by schistosome eggs have been performed using SEA. SEA is a complex mixture of proteins of a potentially variable composition depending on the developmental stage of the eggs and the solubilization procedure used. The properties of such preparations have been studied *in vitro*, e.g. in dendritic cell (DC)/T-cell skewing and signaling assays (de Jong et al., 2002; Kane et al., 2004; Cervi et al., 2004; van Liempt et al., 2007; Everts et al., 2009), and *in vivo*, e.g. by injections into an array of wild type, transgenic and knock-out mice (MacDonald et al., 2001; Breuilh et al., 2007; Vella and Pearce, 1992).

Regardless of the exact composition of the egg-derived molecules or components studied, a significant proportion of the immunological activity associated with *S. mansoni* eggs appears to be mediated by protein-linked glycans. These glycans dictate interactions with receptors of the innate immune system, such as the C-type lectin receptors (CLR), and mediate antigen uptake by

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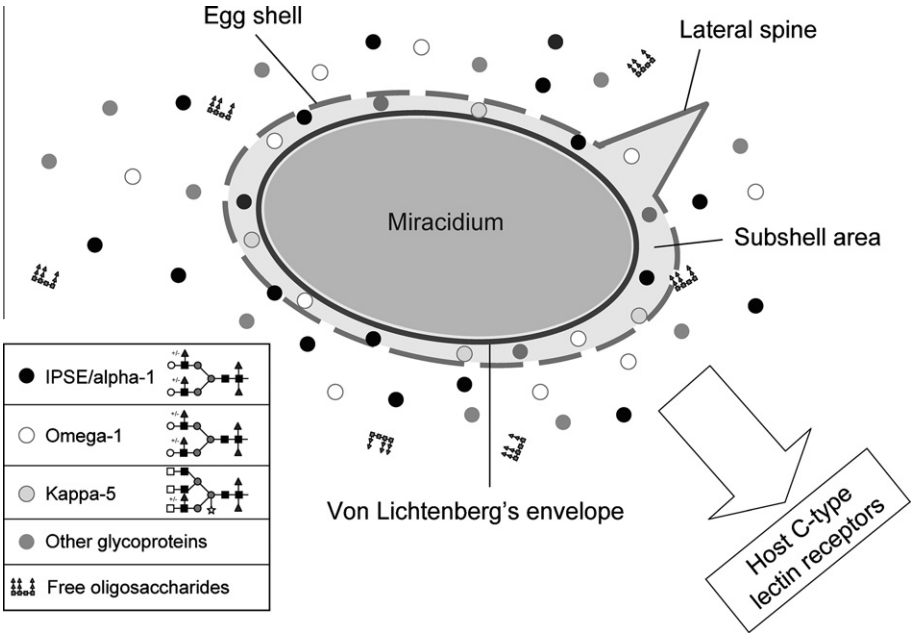

Fig. 1. Schematic overview of the mature *S. mansoni* egg and egg components. Glycan structures in insert: see Table 1.

antigen presenting cells (APC). Egg glycans are also the target of a strong antibody response in schistosome infections and numerous highly antigenic glycan structures have been identified (van Remoortere et al., 2000; Eberl et al., 2001; Kariuki et al., 2008; Nyame et al., 2003). Although highly relevant to the immunology of schistosomiasis, in this review we will not discuss egg glycans as targets of the antibody response but we will focus on glycans of schistosome eggs that interact with CLR of the mammalian host and discuss these interactions in view of egg-induced immune responses.

2. General molecular aspects of SEA

Proteomics studies using 2D-gel electrophoresis and mass spectrometry have shown that over a thousand proteins can be detected in SEA, with a broad range of functions on target cells. These can be exerted either inside (e.g. cytosolic and nuclear proteins) or outside (e.g. membrane proteins, secretory proteins) a cell (Ashton et al., 2001; Mathieson and Wilson, 2010). Although few studies have been conducted on individual SEA glycoproteins, it is clear that many SEA components are glycosylated (Pearce and MacDonald, 2002; Robijn et al., 2005). Glycosylation is a common feature of proteins which pass through the RER and the Golgi-complex, and follow the secretory pathway to the cell surface. N- and O-glycans linked to asparagine and serine/threonine, respectively, are added to the protein backbone via a highly regulated cell- and schistosome life stage-specific process involving the concerted actions of glycosyltransferases and other glycosylation-modifying enzyme activities (Varki et al., 2009). Structural studies on preparations of N- and O-glycans released from the peptide backbones have shown that SEA glycoproteins collectively display a very complex set of glycans, comprising specific schistosome glycans, as well as glycans expressed by the mammalian host (Table 1) (Khoo et al., 1997; Jang-Lee et al., 2007). Each type of glycan or glycan element can be present on a larger subset of SEA glycoproteins (Robijn et al., 2005). SEA includes the excretory/secretory (ES) (glyco)proteins, but it does not contain water insoluble glycoconjugates, including membrane glycoproteins and hydrophobic glycolipids, unless specific solubilization procedures were followed.

Table 1
Typical glycans and glycan elements of *S. mansoni* SEA and ES glycoproteins.

Abbreviation	Structure[a]
LN	
Lewis X	
LDN	
LDN-F	
F-LDN	
F-LDN-F	
LDN-DF	
Multi-fucosylated HexNAc	
Core α3-fucose	
Core β2-xylose	
Major kappa-5 glycans	
Major IPSE/alpha-1/omega-1 glycans	

[a] Dark circle, mannose; light circle, galactose; light square, *N*-acetylgalactosamine; dark square, *N*-acetylglucosamine; dark triangle, fucose; xylose, light star.

3. Immunomodulatory properties of SEA

SEA consistently is an inducer of Th2 responses in different types of experiments either *in vitro* or *in vivo* and both in humans or in animal models. In particular, studies of dendritic cells (DC) have been instrumental in understanding the polarization of immune responses towards Th2 by SEA (MacDonald et al., 2001; de Jong et al., 2002; Kane et al., 2004; Cervi et al., 2004; van Liempt et al., 2007; Jankovic et al., 2004). While DC fail to show classic signs of maturation when stimulated with SEA (MacDonald et al.,