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Compatibility polymorphism in snail/schistosome interactions: From field to theory to molecular mechanisms

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Abstract

Coevolutionary dynamics in host–parasite interactions potentially lead to an arms race that results in compatibility polymorphism. The mechanisms underlying compatibility have remained largely unknown in the interactions between the snail *Biomphalaria glabrata* and *Schistosoma mansoni*, one of the agents of human schistosomiasis. This review presents a combination of data obtained from field and laboratory studies arguing in favor of a matching phenotype model to explain compatibility polymorphism. Investigations focused on the molecular determinants of compatibility have revealed two repertoires of polymorphic and/or diversified molecules that have been shown to interact: the parasite antigens *S. mansoni* polymorphic mucins and the *B. glabrata* fibrinogen-related proteins immune receptors. We hypothesize their interactions define the compatible/incompatible status of a specific snail/schistosome combination. This line of thought suggests concrete approaches amenable to testing in field-oriented studies attempting to control schistosomiasis by disrupting schistosome–snail compatibility.

Keywords

Biomphalaria glabrata; *Schistosoma mansoni*; Host/parasite interaction; Compatibility polymorphism; FREPs; SmPoMucs

1. Introduction

Parasites cause substantial deleterious effects to their hosts, and therefore represent a major driving force in their evolution (Howard, 1991). In parallel, parasites have to cope with host-defence mechanisms to avoid elimination. This reciprocal antagonistic co-evolution between both partners can be illustrated by an arms race in which host and parasite develop mechanisms to circumvent counter-measures developed by their opponent. In certain interactions and at a particular time of their evolution, parasite virulence and host defence can be in equilibrium in natural populations. This can lead to a phenomenon called compatibility polymorphism. Compatibility is a characteristic of a host–parasite system where the parasite species is capable of establishing infection and achieving transmission using this host species (Coustau and Theron, 2004). To achieve compatibility, the parasite has to evade host defense systems in order to complete its life cycle (Sapp and Loker, 2000; Van Der Knaap and Loker, 1990). In certain host–parasite systems, compatibility is

incomplete: sometimes the host wins and the parasite is eliminated, and sometimes the parasite wins and succeeds in infecting the host. This phenomenon is called compatibility polymorphism. It occurs in the interaction between the metazoan parasite *Schistosoma mansoni*, the agent of human intestinal schistosomiasis (Gryseels et al., 2006) and its invertebrate intermediate host, the gastropod mollusk *Biomphalaria glabrata* (see Fig. 1 for life cycle description). Genetic studies conducted with the *S. mansoni*/*B. glabrata* model demonstrated that compatibility is heritable and can be selected in the laboratory, either for susceptibility/resistance of the snails or the infectivity of the parasite (Davies et al., 2001; Richards et al., 1992; Webster et al., 2004). Compatibility may reside in a concordance of genetically determined phenotypes in snail and schistosome, each of which being polymorphic with respect to the relevant trait (Basch, 1975, 1976). Understanding the underlying mechanisms that maintain such sustainable interactions represents a major challenge for both parasitologists and immunologists. Here we review results obtained recently with this host–parasite system with the aim of linking empirical data from field studies to experimental studies focusing on the molecular components of host resistance and parasite infectivity, and their interactions.

2. From field observations to a theoretical framework

Temporal and spatial variation in the degree of compatibility between snails and schistosomes is an important phenomenon of direct relevance to the epidemiology of transmission (Prugnolle et al., 2006). However, a key problem concerning these compatibility studies is that data have been exclusively obtained from one or several generations of laboratory bred snails and/or schistosome strains passed through laboratory definitive hosts. Consequently they are poorly representative of the genetic variation present in their original populations. A limited initial sampling of the diversity present in the field, laboratory host-induced selection, founder effects and bottlenecking processes during lab maintenance have been demonstrated to sharply reduce genetic diversity in laboratory strains, particularly for the parasite (Bech et al., 2010; Stohler et al., 2004).

Recently, for the first time, snail–schistosome compatibility was investigated using both field-derived miracidia and snails from the same geographic locality (Guadeloupe) and in optimized conditions: numerous naturally infected definitive hosts were used as sources of miracidia, and varying doses of miracidia per host were used for snail exposures. This protocol took into account the great extent of parasite and host genetic diversity present in the natural populations (Theron et al., 2008). Dose–response curves showed that infection rates increased with increasing doses of parasites (from 1 to 20 miracidia per host) and reached 100% infection up to a dose of 10 or 20 miracidia (Fig. 2). Snails and parasites from this same geographic source were then used to establish laboratory strains, and compatibility was tested during several successive laboratory passages. In the transition from field to lab, compatibility dropped from 100% to around 50% after the first laboratory generation (Fig. 2). This compatibility level remained relatively stable during the entire time the parasite strain was maintained (from 2005 to present), while the neutral genetic diversity of the schistosome strain declined steadily (Bech et al., 2010).

There is a large difference between compatibility levels observed under wild vs. laboratory conditions. First, all wild snails become infected if exposed to enough wild miracidia. We hypothesize this is because the probability of a match (infection) increases with the dose of miracidia simply because a larger fraction of the phenotypic diversity present in the parasite population is included. All *B. glabrata* are potentially susceptible to *S. mansoni*, and will develop a patent infection if given enough genetically diverse miracidia. Reciprocally, we speculate that all *S. mansoni* miracidia are potentially infective, if they are exposed to the right individual snail with a matching genotype, although this experiment is difficult to

undertake because the same miracidium cannot be exposed to multiple snails. The low natural snail prevalence of snails with patent schistosome infection that is usually observed in transmission foci (Anderson and May, 1979; Sire et al., 1999) is then potentially due to the low probability that a schistosome phenotype encounters its corresponding compatible host phenotype rather than the existence of high level of resistance within host populations. The drop in compatibility after laboratory passage may result from a relatively more severe genetic bottleneck in the parasite (Bech et al., 2010; Stohler et al., 2004; Theron et al., 2008) than the host (Campos et al., 2002; Mulvey and Vrijenhoek, 1981). The parasite strain exhibits a reduced set of phenotypes that match only with a fraction of the phenotypes present in the host strain (Theron and Coustau, 2005). Even with high doses of miracidia per snail (Theron et al., 2008), there are some lab reared snails that will never become infected with this laboratory strain of parasite (Fig. 2). They would however, potentially remain susceptible to another schistosome strain that has retained a different set of matching phenotypes.

Another important finding in snail–schistosome interactions concerns the different fate of individual parasites that all penetrate the same snail. From histological sections of snails exposed to 20 miracidia, it was observed that an infected snail may have both developing and encapsulated primary sporocysts side by side within the tissues (Theron et al., 1997). This means that infectivity appears not to be a general characteristic of the parasite. The phenotype (infective vs. uninjective) of a parasite is expressed as a function of the genotype of the particular host that it enters. Conversely, susceptibility appears not to be a general characteristic of the host. The phenotype (susceptible vs. unsuitable) of a host is expressed as a function of the parasite genotype it harbors. Previous exposures to other species of parasites may further modify the host phenotype through activation or inhibition of immune function (Lie, 1982; Lie et al., 1982). Based on such phenotype-by-phenotype interaction (Basch, 1975) the various levels of compatibility observed in the field and in the laboratory will be highly dependent of the phenotypic composition present in the host and parasite sample used and may result in infection rates varying from 0% to 100% (Theron and Coustau, 2005). A matching phenotypes model is believed to be based on a system of self/non-self recognition or mimicry molecules and a particular effort has been made recently to identify putative interacting molecular determinants and genomic processes that generate their diversity. This would conform to general theoretical ideas that immunological interactions between hosts (including invertebrates) and parasites can exhibit considerable specificity (Schmid-Hempel and Ebert, 2003).

3. From theoretical framework to molecular mechanisms

3.1. Identification of the *S. mansoni* polymorphic mucins (SmPoMucs)

A comparative molecular approach was first developed using two *S. mansoni* laboratory strains: one, totally compatible (C strain) and the other totally incompatible (IC strain) towards the same (Brazilian strain) *B. glabrata* (Fig. 3). Newly penetrated parasites from the IC strain are contacted by host hemocytes within 1 h post-infection and entirely encapsulated by 4–8 h post-infection (Fig. 3). In contrast, newly-penetrated miracidia of the C strain were not encapsulated and primary sporocyst (Sp1) developed normally (Fig. 3). These observations suggested that constitutive antigenic differences exist between the two strains, which have since been investigated using a comparative proteomics approach (Roger et al., 2008c). The main difference evidenced between the C and IC *S. mansoni* strains concerns a family of schistosome antigens that share characteristics with molecules of the mucin family (Roger et al., 2008c). They were named *S. mansoni* polymorphic mucins (*SmPoMuc*).

SmPoMuc precursor structure and expression analysis showed that these proteins display a mucin-like structure with an N-terminal domain containing a variable number of tandem repeats (VNTR) (Roger et al., 2008a). *SmPoMuc* proteins are: (i) highly glycosylated, (ii) only expressed by larval schistosome stages that interact with the snail intermediate host, (iii) located in the apical gland of miracidia and sporocysts, (iv) secreted and released in excretory–secretory products and finally (v), highly polymorphic (Roger et al., 2008a).

A detailed analysis of their high level of intra- and inter-strain variation showed that *SmPoMuc* polymorphism is driven by a complex cascade of mechanisms (Roger et al., 2008b) that is illustrated in Fig. 4. *SmPoMucs* are encoded by a multigene family of around 10 members that occupy four loci in the genome of *S. mansoni* (Roger et al., 2008b). Frequent recombination events generate new alleles. Several mechanisms generate additional levels of polymorphism of expressed sequences. First, individual Sp1 larvae, both within and between the C and IC strains of *S. mansoni*, express uniquely specific subsets of *SmPoMuc* genes. Some individuals express only one gene, whereas others express several genes in combinations that differ among individuals. Second, transcripts are modified by frequent trans-splicing, alternative splicing and aberrant splicing events (Roger et al., 2008b). The mechanisms controlling the expression polymorphism of *SmPoMucs* are currently under investigation. The involvement of epigenetic mechanisms is considered highly likely. Indeed, Trichostatin-A a modifier of chromatin organization has been shown to modify *SmPoMuc* transcription patterns (Cosseau et al., 2010).

A combination of *in silico* analysis of the predicted glycosylation patterns of *SmPoMuc* sequence variants and of chemical deglycosylation experiments to determine overall glycosylation levels indicated that sequence polymorphism is directly linked to glycosylation status. Indeed, we found quantitative and qualitative differences between carbohydrate patterns of *SmPoMucs* between strains. *SmPoMuc* of the IC strain were more heavily glycosylated than *SmPoMucs* recorded from *S. mansoni* C strain (Roger et al., 2008b). The superimposition of these different levels of variability provides an extraordinary level of polymorphism for *SmPoMucs* that we have termed “controlled chaos”.

A remarkably high degree of polymorphism for *SmPoMucs* is generated from a limited set of genes (Roger et al., 2008b), in a fashion that appears unique for this model compared to mechanisms that lead to the expression of polymorphic molecular variants by other genera of parasites. Indeed, in all previously described cases, the molecular variants are synthesized from a large set of genes. One example is the case of *Trypanosoma cruzi* surface mucins (see (Buscaglia et al., 2006) for review) that contribute to protection of the parasite against host responses and to the establishment of a persistent infection. The multigene family encoding these proteins comprises 850 genes, covering no less than 1% of the parasite genome. Other relevant gene families include the *vsg* and the *var* families responsible for antigenic variation of *Trypanosoma brucei* (Navarro et al., 2007; Taylor and Rudenko, 2006) and *Plasmodium falciparum* (Kyes et al., 2007; Ralph and Scherf, 2005), respectively. The *T. brucei* genome contains more than 1000 *vsg* genes and pseudogenes and the genome project of *P. falciparum* identified 59 intact *var* genes.

3.2. *SmPoMucs* antigenic variants are recognized by diversified *B. glabrata* immune receptors

The structure, expression pattern, and inter- and intra-strain polymorphism made the *SmPoMucs* promising candidates as key determinants of the compatibility polymorphism in the interaction between *S. mansoni* and *B. glabrata*. Another proteomic analysis strengthened this hypothesis. This latest approach was dedicated to the characterization of the interactome between *S. mansoni* extracts and plasma from *B. glabrata*. *SmPoMucs* and

other glycoproteins from *S. mansoni* were found to interact and precipitate with several *B. glabrata* proteins. Among the interactive snail-derived proteins were lectins of the FREP (fibrinogen-related proteins) gene family (Adema et al., 1997). FREPs are encoded by a multigene family of at least fourteen members (Zhang and Loker, 2004; Zhang et al., 2008a). They consist of one or two amino-terminal IgSF (Immunoglobulin Super Family) domains joined to a carboxyl-terminal fibrinogen domain. The diverse genes encoding the FREP molecules undergo somatic modification involving gene conversion and point mutations, leading to a remarkable degree of diversification (Zhang et al., 2004). The superimposition of allelic polymorphism and somatic processes can lead to the expression of 36 amino acid sequence variants of FREP3 per individual snail (Zhang et al., 2004). These molecules are hemolymph lectins that precipitate soluble antigens derived from trematodes (Adema et al., 1997), bind to sporocysts of another trematode parasite, *Echinostoma paraense* and a variety of microbes (Zhang et al., 2008b), and have opsonic properties (Hanington et al., 2011). Knock-down of FREP3 by siRNA-mediated interference rendered approximately 30% of normally resistant adult snails susceptible to *E. paraense*, providing the first example of a specific snail immune gene shown directly in a functional assay to alter the phenotype of susceptibility (Hanington et al., 2011). This study also provided evidence that the array of FREP3 molecules produced differs among subsets of hemocytes, carrying the implication that all hemocytes of *B. glabrata* are not functionally equivalent. An attractive hypothesis is to consider that the variability inherent in FREPs, especially given their emerging functional role in influencing the outcome of trematode infection, provides a host-based system that matches and potentially counters the variability inherent in *SmPoMucs*. We argue that the interactions of FREPs and *SmPoMucs* provide an excellent system to explore as the molecular basis for the compatibility polymorphism between *S. mansoni* and *B. glabrata*. One missing piece in this story has been the nature of the ligands bound by FREPs. Recent co-immunoprecipitation experiments were undertaken using antibodies raised specifically against *SmPoMuc*. They showed that FREP2 co-immunoprecipitated with *SmPoMucs*, providing additional supportive evidence for our hypothesis. *FREP2* is a member of the *FREP* gene family that is consistently and markedly up-regulated following exposure of *B. glabrata* to *S. mansoni* (Adema et al., 2010; Hanington et al., 2010; Hertel et al., 2005). Moreover, an analysis undertaken in Perpignan revealed that FREP2 is probably also subject to somatic diversification as well, just as had been observed with FREP3 earlier, and as recently confirmed (Adema et al., 2010; Hanington et al., 2010; Hertel et al., 2005). Thus, FREP2 may also exist in a large repertoire of variant molecules as shown for FREP3. Consequently, FREP2 could represent a diversified receptor population that is dedicated to recognition of parasite determinants in case of a schistosome infection. The concept that molluscan defense molecules can be highly diversified has also been recently supported by studies of *Mytilus* antimicrobial peptides (Costa et al., 2009).

In addition, another interesting snail factor that co-immunoprecipitated with the molecular complex that comprised FREPs and parasite extracts, was a putative opsonin, the ThioEster-containing Protein from *B. glabrata* (BgTEP). Precursor and phylogenetic analysis suggest that BgTEP shares features of invertebrate TEPs (Mone et al., 2010) that are known to be involved in antiparasitic defence and microbe phagocytosis (Blandin and Levashina, 2004, 2007; Blandin et al., 2008; Stroschein-Stevenson et al., 2006). LC-MS/MS experiments led to the identification of peptides that were all located exclusively in the C-terminal part of BgTEP (Mone et al., 2010). This suggests that BgTEP had been cleaved before association of its C-terminal part with the two other partners of the complex. This kind of cleavage has been described for numerous members of the TEP family during their activation, especially for TEP1 from mosquitoes (Levashina et al., 2001). Therefore, precipitate- derived BgTEP is probably activated and could play a role in opsonisation. This hypothesis is supported by the Alpha2 Macroglobulin receptor binding domain (region 1343–1427) in the C-terminal

part of the BgTEP precursor (Mone et al., 2010). Comparable domains are known to interact with specific receptors of macrophages and phagocytes (van Lookeren Campagne et al., 2007).

4. Conclusion

The data recently obtained and reviewed above argue in favor of a key role for *SmPoMucs* and FREPs in the compatibility polymorphism between *S. mansoni* and *B. glabrata*. Among the different molecules identified by the combination of approaches reviewed here, at least thus far, it appears that FREPs and *SmPoMucs* display the appropriate level of polymorphism to explain the compatibility polymorphism in *B. glabrata/S. mansoni* natural populations. The conceptual scheme of matching phenotypes that was deduced from population level studies supports the view that two repertoires of highly polymorphic molecules from host and parasite are deployed against one another during the early stages of the process of infection, and this interaction is a key component of dictating the success or failure of the infection. In the approach dedicated to the study of *SmPoMucs* expression (Roger et al., 2008a), we hypothesize that *SmPoMucs* are released during larval transformation. This hypothesis was deduced from (i) the structure of the precursor that contains a putative N-terminal signal peptide, (ii) Western blot experiments revealing *SmPoMuc* immunoreactivity in excretion/secretion products (ESP) of sporocysts maintained in culture medium and (iii) the immunolocalization of *SmPoMucs* in apical glands involved in ESP synthesis. This combination of evidences leads us to hypothesize that *SmPoMucs* might create an immunological smoke-screen by generating antigen-antibody complexes away from the parasite as suggested for other helminths (Loukas et al., 2000; Marin et al., 1992). Nevertheless and as mentioned above, we showed recently that *SmPoMuc*/FREP complexes are formed using strains of *B. glabrata* and *S. mansoni* that are totally incompatible (Mone et al., 2010). In addition and in the same paper, we showed that a third molecular partner is present in the complex, the TEP whose presence and structure argue clearly in favor of a role of this complex in the encapsulation process that occurs in incompatible combination. All these data taken together allow us to propose the model shown in Fig. 5. *SmPoMucs* and FREPs are polymorphic molecules with individual-specific patterns of expression. Both are retrieved in the same immune complex together with BgTEP, an excellent candidate to facilitate involvement of cellular effectors by serving as an opsonin. BgTEP may associate with FREPs that have bound parasite factors and then recruit hemocytes through its Alpha2 Macroglobulin receptor-binding domain interacting with a (as yet to be identified) specific receptor present on hemocyte surfaces. FREPs may also play a direct opsonic role (Hanington et al., 2011) in this interaction. In a compatible combination, *SmPoMucs* are not recognized by the internal defences of *B. glabrata* and encapsulation of *S. mansoni* does not occur. This recognition default could be due to antigen mimicry (e.g., glycan sharing) that have been already suggested (Chacon et al., 2002; Lehr et al., 2008; Peterson et al., 2009; Yoshino and Bayne, 1983) and whose molecular determinants could be *SmPoMucs*. In an incompatible combination, an immune complex composed of *SmPoMucs*, FREPs and BgTEP is produced. The consequence would be the rapid formation of a hemocyte capsule that surrounds the sporocyst and results in killing of the parasite. We should also be open to the possibility that FREPs may play a direct harmful role on sporocyst development, for example by preventing growth or assimilation of nutrients, or preventing asexual reproduction. *SmPoMucs* of the right constitution might interfere with this function.

5. Perspective

The hypothesis proposed herein suggests several further lines of inquiry. First, the full composition of the immune complexes and the actual domains of the host and parasite

protein that interact with one another remain to be fully characterized. This characterization is crucial to understand which combinations of molecular determinants define the compatibility or incompatibility status of the interaction. This will be particularly difficult with respect to the identification of the glycan part of *SmPoMucs* interacting with other proteins of the complex. Nevertheless, two complementary approaches can be envisioned. The first involves co-immunoprecipitation experiments with full length or truncated recombinant FREPs and TEP incubated with sporocyst extracts (containing *SmPoMucs*) to define precisely the FREPs and TEP domains involved in the interaction. For the second approach, the *SmPoMuc* allelic variants available in compatible and incompatible combinations provide an excellent comparative framework to dissect the nature and composition of complex formation. Both approaches could allow identifying FREPs/*SmPoMucs* combinations leading to compatibility/incompatibility”.

As a second line of inquiry, the post-translational processing of BgTEP during the course of infection and the binding of a complex of both FREP and cleaved TEP to the sporocyst surface has to be demonstrated. It was recently shown that Bge cells (a cell line originally derived from *B. glabrata* embryos) express BgTEP (data not shown): this *in vitro* cellular system will be useful to address these questions. Third, additional RNAi knock-down experiments targeting BgTEP are needed for functional studies. The feasibility of this methodology was confirmed independently by several research groups (Baeza Garcia et al., 2010; Hanington et al., 2011; Jiang et al., 2006; Knight et al., 2011). Lastly, also needed are studies to document specifically how *SmPoMuc*–FREP–TEP complexes specifically engage hemocytes to initiate encapsulation.

It is important to note that our proposed hypothesis represents one particular line of thought, and that other molecules may well be involved in the compatibility polymorphism phenomenon. Several recent studies have shown that ROS and ROS scavengers as well as other glycoprotein/lectin partners (Bender et al., 2007; Ittiprasert et al., 2010; Mone et al., 2010; Mourao et al., 2009; Yoshino et al., 2008) play a role in the outcome of sporocyst–hemocyte interactions. All these data taken together suggest that the mechanism underlying compatibility polymorphism between *S. mansoni* and *B. glabrata* is multifactorial and likely varies among populations. Further comparative studies should investigate these different factors in different populations of *Biomphalaria* snails and their schistosome parasites that have different co-evolutionary histories. These population level studies will be crucial to understanding the complexity of this phenomenon at a worldwide scale. It is also important to determine if the molecules we hypothesize are involved in dictating compatibility are involved in natural transmission foci of schistosomiasis. For example, can some *Biomphalaria* snails from habitats actually supporting *S. mansoni* transmission mount FREP responses that can overcome the protective “smoke screen” of local *SmPoMucs* and prevent infection and the eventually shedding by that snail of huge numbers of human-infective cercariae? Furthermore, can we manipulate these responses in ways to prevent snail infections from occurring?

Also important to achieving an overall understanding of trematode– snail interactions is to bear in mind that it is not uncommon for a snail, such as *B. glabrata*, to encounter multiple trematode species in its environment, some of which may be more common than *S. mansoni*. Do these parasite species also deploy polymorphic molecules to frustrate recognition, and how does a population of snails potentially hedge its defence bets in an environment supporting multiple types of parasites? By continuing to exploit the advantages of the *S. mansoni*–*B. glabrata* model, we will someday gain a broader insight into these questions as well.

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Box 1**Key Learning Points**

- The reciprocal antagonistic co-evolution of hosts and parasites can result in a compatibility polymorphism for which the underlying mechanistic operation remains largely unknown.
- Combined data from recent field and laboratory studies lead us to propose a matching phenotype model to explain the compatibility polymorphism phenomenon in the interaction between *B. glabrata* and *S. mansoni*.
- Molecular approaches dedicated to the identification of the underlying immunological mechanisms led to the discovery of polymorphic and/or diversified molecular determinants: the FREPs of *B. glabrata* and the *SmPoMucs* of *S. mansoni*.
- FREPs and the *SmPoMucs* have been shown to interact with one another, and thus are appropriate candidates to explain compatibility polymorphism. They could constitute two molecular repertoires from host and parasite that are deployed against one another to determine the success or failure of the infection.

Box 2**Five Key Papers in the Field**

1. Basch, P.F., 1975. An interpretation of snail–trematode infection rates: specificity based on concordance of compatible phenotypes. *Int. J. Parasitol.* 5, 449–452.
2. Coustau, C., Theron, A., 2004. Resistant or resisting: seeking consensus terminology. *Trends Parasitol.* 20, 209–210.
3. Zhang, S.M., et al., 2004. Diversification of Ig superfamily genes in an invertebrate. *Science* 305, 251–254.
4. Roger, E., et al., 2008. Controlled chaos of polymorphic mucins in a metazoan parasite (*S. mansoni*) interacting with its invertebrate host (*B. glabrata*). *PLoS Neglected Trop. Dis.* 2, e330.
5. Mone, Y., et al., 2010. A large repertoire of parasite epitopes matched by a large repertoire of host immune receptors in an invertebrate host/parasite model. *PLoS Neglected Trop. Dis.* 4.

Fig. 1.

Schistosoma mansoni life cycle. The genus *Schistosoma* currently contains 22 species, three of which, *S. haematobium*, *S. japonicum*, and *S. mansoni* are the principal agents of human schistosomiasis, the world's second most important parasitic disease after malaria. It infects 210 million people and is estimated to kill over 200,000 persons each year (Chitsulo et al., 2004). Schistosome parasites (Digenea) have a complex life cycle that involves two hosts (see life cycle). Adult worms mate in the venous system of a vertebrate host. They produce eggs that are expelled with the feces or urine. If deposited in an aquatic environment, the eggs hatch to release a miracidium that will infect specific species of freshwater snails. Inside the snail tissues, the miracidium transforms into a primary sporocyst (Sp1) that multiplies asexually to produce secondary sporocysts (Sp2), which then produce cercariae. Cercariae leave the snail and actively infect the vertebrate definitive host.

Fig. 2.

Schistosoma mansoni/Biomphalaria glabrata from field to laboratory compatibility. Change in levels of compatibility when using (a) wild-type parasites and wild-type snails directly collected from the field and (b) their derived respective strains when established in the laboratory. Infection rates are enumerated after individual exposure of snails to increasing doses of *S. mansoni* miracidia (Mi). The observed reduction in compatibility (arrows) may be explained under the hypothesis of a matching phenotype model of interaction (symbols represent phenotype diversity for compatibility between *Biomphalaria* snails and *S. mansoni* parasites). Due to laboratory conditions of maintenance, the parasite strain exhibits a reduced set of phenotypes that match only with a fraction of the host phenotypes (modified from Theron et al. (2008, 2004)).

Fig. 3.

Schistosoma mansoni/Biomphalaria glabrata immunobiological interactions. The outcome of the infection process is dependent on the compatibility of the individual host and parasite in interaction. Compatible (C) or InCompatible (IC) strains of *Schistosoma mansoni* towards the same mollusc strain were selected in the laboratory in Perpignan. Parasites of the IC strain (picture A), were recognized immediately after penetration, encapsulated and killed by the hemocytes, the snail's circulating immune cells. A multi-layer hemocyte capsule surrounds a dead sporocyst at 24 h after penetration. A parasite of the C strain (picture B), was not recognized and developed normally in snail tissue. The sporocyst is growing in the snail foot 24 h after penetration.

Fig. 4.
The *SmPoMucs* polymorphism: a controlled chaos.

Fig. 5.

Our hypothetical scenario that leads to compatibility/incompatibility in *Schistosoma mansoni*/*Biomphalaria glabrata* interactions. In a compatible combination, *SmPoMucs* are not recognized by FREPs and encapsulation does not occur. In an incompatible combination, the immune complex composed of *SmPoMucs*, FREPs and BgTEP is produced. BgTEP, after activation by cleavage functions as opsonin and recruits hemocytes through their Alpha-2-Macroglobulin receptor (A2MR) that binds to the A2MR binding domain in the C-terminal part of BgTEP. As a consequence, a hemocyte capsule develops around the sporocyst, and effects to parasite killing.