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SEX DETERMINATION AND FEMALE REPRODUCTIVE DEVELOPMENT IN THE GENUS *Schistosoma*: A REVIEW

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SUMMARY

Parasites of the genus *Schistosoma* were among the first metazoans to develop separate sexes, which is chromosomally determined in the fertilized egg. Despite the occurrence of specific sex chromosomes, the females of most Schistosomatidae species do not complete their somatic development and reach no sexual maturity without the presence of males. Indeed, the most controversial and at the same time most fascinating aspect about the sexual development of *Schistosoma* females lies on discover the nature of the stimulus produced by males that triggers and controls this process. Although the nature of the stimulus (physical or chemical) is a source of controversy, there is agreement that mating is a necessary requirement for maturation to occur and for migration of the female to a definitive final site of residence in the vascular system of the vertebrate host. It has also been proposed that the stimulus is not species-specific and, in some cases, not even genus-specific. Despite a vast literature on the subject, the process or processes underlying the meeting of males and females in the circulatory system have not been determined and as yet no consensus exists about the nature of the stimulus that triggers and maintains female development. In the studies about their role, *Schistosoma* males have been considered, at times pejoratively, the brother, the muscles or even the liver of females. Indeed, it still remains to be determined whether the stimulus responsible for female maturation involves the transfer of hormones, nutrients, neuromediators, mere tactile stimulation or a combination of chemotactic and thigmotactic factors.

KEYWORDS: *Schistosoma;* Sex determination; Sex maturation; Female development; Reproductive development; Male development.

INTRODUCTION

Parasites of the genus *Schistosoma*, by being dioic, were among the first metazoans to develop separate sexes, thus representing an exception among trematodes of the Digenea subclass, whose members are hermaphrodites[72, 80, 86, 89]. The current dioic characteristic may have resulted from a gradual or abrupt evolutionary process from the protandry or protogyny stage reached by the hermaphrodite ancestors (proto-schistosomes). With the separation of the sexes and the consequent need for cross fertilization, the evolution of schistosomes must have been accelerated by the joining of the genomes of males and females parasitizing different hosts such as birds, migratory mammals, or even reptiles of the mesozoic era[7, 74]. The occurrence of specific sex chromosomes, however, did not garantee complete female somatic development, nor sexual maturity and, for most of the *Schistosoma* species, the female development can only be fully accomplished in the presence of males[7, 30, 57, 74].

The different hypothesis formulated to explain the nature of the stimulus that determines and controls the somatic and reproductive development of females may be grouped into four categories: 1 – insemination or transfer of substances with sperm, 2 – nutritional supplementation, 3 – hormonal influences, and 4 – tactile stimulation[61, 102]. In this review we shall analyse the different hypothesis concerning the *Schistosoma* female sexual development highlighting the role played by the male in this process.

SEX DETERMINATION

The hypothesis that sex may be chromosomally determined in the genus *Schistosoma* was raised at the beginning of the century and gained support with the study published by CORT[24] in 1921. On the basis of his own observations and as well as of others, the author proposed that "sex in schistosomes is determined in the fertilized egg and all the cercariae coming from a single miracidium are of the same sex".

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The determination of the occurrence of sex chromosomes in the family Schistosomatidae, however, was preceded by a long period of speculation about the exact number of chromosomes in the schistosomes which lasted throughout the first half of the century[45, 64, 107]. Only with the advances in cytogenetic techniques (Giemsa staining and C-banding techniques) did it become possible more precisely to establish a karyotypic pattern for *S. mansoni* and other species in the family Schistosomatidae.

In 1960, SHORT & MENZEL[112] reported that the diploid chromosome number of nine species of schistosomes was 16, as confirmed in later studies[110, 111, 113]. A series of studies were carried out since using cytogenetic techniques of higher resolution to define or compare the karyotypes of different species in the family Schistosomatidae[4, 37, 38, 56, 109, 110, 111, 114].

Up to the 1960's prevailing view was that male schistosomes corresponded to the heterogametic sex, with females thus being homogametic[71]. In a study of meiotic chromosome preparations (pachytene squashes), MENZEL & SHORT (1960)[60] suggested the occurrence of heteromorphic sex chromosomes (XY) in females of *Schistosomatium douthitti* and *Ornithobilharzia mansoni*. The occurrence of Barr bodies in interphase nuclei of *S. mansoni* cercariae was later reported. Cercariae that developed into males presented two Barr bodies, whereas cercariae that gave origin to females had only one Barr body[83]. Subsequent studies confirmed these findings and established the fact that the females correspond to the heterogametic sex[37, 39, 110]. ATKINSON (1980)[4] proposed the ZW representation for heterogametic schistosome females in accordance with the nomenclature rules established for other species such as frogs, birds and butterflies[11, 70, 132].

SEX MATURATION OF FEMALES

The first reference to this aspect of the biology of schistosomes was part of the observations attributed by CORT (1921)[24] to YOKOGAWA (unpublished results). This researcher, by inoculating *S. japonicum* cercariae from a single mollusk previously infected with one miracidium, obtained unisex infections in which the worms did not reach somatic or reproductive maturity.

The systematization of the study on the sexual development of females started with the studies of SAGAWA et al. (1928)[92] and SEVERINGHAUS (1928)[97], in which was shown that *S.japonicum* females from unisex infection did not reach reproductive maturity and presented a smaller body size than that of females from bisexual infections. This phenomenon was later described for other species of the genus *Schistosoma* such as *Schistosoma haematobium*, *S. bovis* and *S. mansoni*[15, 58, 62, 128].

Before continuing the discussion of this intriguing and still polemic aspect of the biology of schistosomes, it should be pointed out that in other genera of the family Schistosomatidae such as *Schistosomatium douthitti* and *Heterobilharzia americana* the females show less dependence on males[106, 108, 123]. However, even though the unmated females of these species present normal sexual development, their body size continues to be smaller than that of mated females[2]. *S. mattheei* females represent the only well established exception within the genus since they can develop and produce eggs in the absence of males, although the eggs produced in general are nonviable[122]. A recent publication[51] reported that eggs with motile miracidia were obtained from unisexual females of *S. haematobium* parasitizing hamsters, in contrast to results previously reported by SAHBA & MALEK (1977)[93] who only obtained infertile eggs and nonviable miracidia in mice. According to the interpretation of KHALIL & MANSOUR (1995)[51], *S. haematobium* females may also present full parthenogenesis and the discordance between these two reports may be due to the differential susceptibility of the hosts (hamster/mouse).

A series of morphological-comparative studies of females from uni- and bisexual infections has been conducted over the years. Although the differences in body weight are the most obvious ones, changes at the microscopic level have been documented. ERASMUS (1973)[27] carried out a detailed comparative study at the ultrastructural level between females from uni- and bisexual infections with *S. mansoni* in which he observed, among other findings, that unisexual females presented immature vitelline cells as well as incomplete development of Mehlis glands and ovaries. These findings were later confirmed in other reports[30, 100, 102]. These degenerative alterations observed in the vitelline gland and ovary were similar to those detected in paired females kept in *in vitro* cultures[43, 44, 46, 47].

As expected, the structural alterations were accompanied by, or rather, were due to a series of metabolic alterations observed in unmated females whose primary determinant probably was the absence of some physical and/or chemical stimulus supplied by the male. Comparative analyses of Ca, P, K, Mg and S content between females from single and mixed infections showed that the amount of calcium was significantly lower in unisexual females than in females from mixed infections. The amount of the other elements was similar for females from both single and mixed infections[99, 101]. Antigenic differences between females from single and mixed infections have also been reported[3].

Some characteristics related to nutrient uptake among females from single and mixed infections are discussed below.

MALE DEVELOPMENT

There seems to be, if not a consensus, at least a strong current in the literature proposing the fact that male development occurs normally whether or not females are present[30], although physiological and antigenic alterations have been reported among males from uni- and bisexual infections such as increased utilization of aspartic acid among unmated males[20] and qualitative differences in the humoral response to glycoprotein between males from uni- and bisexual infections[3]. It has also been reported that males from unisexual infections are more active[98].

Classically, two well documented exceptions have been reported for the subfamily Schistosomatidae: males of *S. japonicum* from unisexual infections grow more slowly and show a smaller body size[53, 97] and males of *Heterobilharzia americana* remain slender and straighter than paired males[54]. It has been postulated that in these particular cases male development may be controlled at least in part by females[2, 51]. More recently, KHALIL & MANSOUR (1995)[51] reported a considerably significant reduction in body weight among *Schistosoma mansoni* and *S. haematobium* males from unisexual infections. This aspect of schistosome biology deserves reconsideration in view of these new findings.

WHAT DO MALES DO?

Indeed, the most controversial and at the same time most fascinating aspect about the sexual development of *Schistosoma* females is to discover the nature of the stimulus produced by males that triggers and controls this process. As PAUL BASCH (1990)[7] asked: "What does the male *Schistosoma* really do?"

The reply to this intriguing question has been pursued for several decades. Today it is accepted that the male stimulus is necessary not only for females to achieve their full somatic development and reproductive maturity, but also for them to remain in this condition[7, 29, 30, 57, 75].

Sexually mature (adult) females of *S. mansoni* from bisexual infections, when transplanted surgically to different hamster strains or Nile rats (a fact that would simulate unisexual infection), start to present degenerative alterations in worm size, vitelline gland and ovary. These changes were observed by light microscopy in the vitelline glands at 3 days and in the ovary at 6 days post-transplantation[18]. In an electron microscopy study, atypical vitelline cells were detected on the 2nd day post-transplantation. Both the ovary and the vitelline cells presented disorders in cell differentiation and turnover as well as large-scale cell death[80].

Similar results have been obtained using another approach. Animals with mixed *S. mansoni* infections were treated with oxamniquine, a fact that resulted in differential mortality between parasite sexes. Some females of the residual worm population remained unpaired and showed reduced body weight as well as degenerative alterations of the vitelline glands[82]. It may be questioned whether the degenerative changes observed were due to the deleterious effects of oxamniquine on the parasite. This hypothesis, however, proved to be improbable when a new series of experiments was performed in which the females presenting the degenerative alterations cited above at the somatic and reproductive level were paired and transferred to recipients hosts (Nile rats). On the 3rd day post-transplantation these females presented unequivocal signs of somatic development and sexual maturation[79].

These results confirmed data obtained by others, demonstrating that the degenerative alterations presented by female schistosome in the absence of males are reversible since when these females were paired they recovered body growth and reproductive activity even after months of involution[18, 98].

According to MOORE et al. (1954)[62], the main stimulus for sexual maturation of *S. mansoni* females may be supplied by the males during fertilization. At present, the sex maturation of females and their oviposition rates are not considered to be dependent on intact testes, viable sperms or any other substance secreted together with the sperm[61, 102]. Males that become anorchid after X-ray treatment or surgical transection can stimulate the egg-laying and maturation of females as efficiently as intact males[2, 61]. Other investigators have shown that female development may occur in the absence of sperm in the oviduct[8, 27]. It has also been observed that both paired and unpaired females from bisexual infections, when transplanted from mice to recipient hamsters presented sperms in their fertilization chambers, but unpaired females presented degenerative alterations, and formed eggs were seen only in paired females[18].

The hypothesis that the sex maturation of females depends on the transfer of a hormone produced by males was first raised in the 1920's[92, 97], but the hormonal hypothesis gained strength with the later discovery of pheromones in insects[50] and, on the basis of observations made in the animal kingdom as a whole, was considered to be an attractive proposition to explain the sexual development of schistosome females[2, 103]. The hormone ecdysone, which is related to regulation of the molt cycle and plays a key role in the formation of insect eggs[1, 12, 13, 42, 49, 63, 69, 96], was also detected in *S. mansoni* males and correlated with the development and sexual maturation of females[65, 66, 67, 91, 128]. Recently, GIANNINI et al. (1995)[36] observed that innoculating Tamoxifen in hamsters infected by *S. mansoni* resulted in somatic alterations of the parasites females and their eggs.

The more general hypothesis about the possible transfer of some product synthesized by males, with the consequent sexual development of females, involves not only hormonal participation but also the transfer of nutrients such as glucose[21, 22, 23], cholesterol[43, 75, 78], polypeptides and glycoproteins[10, 40], or some type of messenger such as a neuropeptide[115]. According to some investigators, male/female contact may result in alterations of the characteristics of permeability and nutrient uptake in specific regions of the female tegument. These changes may occur rapidly and in specific regions[29, 81]. Some experimental data favor this hypothesis. A 35 to 40% increase in [^{3}H]-thymidine, which represents an indirect measurement of DNA synthesis, was obtained after unpaired females of *S. mansoni* were placed in contact with males[25, 26]. Pairing of females from single sex infections with male worms also resulted in an elevation of [^{3}H]-tyrosine uptake[81]. Considering that tyrosine is avidly taken up by vitelline cells[28], this parameter was proposed as a possible criterion to assess the sexual development of females[81]. Indeed, histochemical analyses have shown that vitelline cells, in addition to nutrient stores for embryo development, also present globules containing precursor egg wall material[117, 133]. The

process of egg wall formation is thought to involve oxidation of tyrosine residues to quinones under the action of the enzymatic system phenoloxidase[16, 19, 31, 68, 84, 87, 130, 136]. Being highly unstable molecules, the quinones may react with amino and sulfhydryl groups of adjacent proteins, leading to the formation of a rigid wall or protective capsule[19, 94, 131, 136].

Still within the context of the possible transfer to females of a product synthesized by males, ATKINSON & ATKINSON (1980)[5] reported the existence of a 66 kDa polypeptide that is synthesized by males and transferred to females. The absence of this polypeptide in females or its transfer to them has not been confirmed in other studies[76]. SHAW et al. (1977)[102] also suggested that females from unisexual infections were stimulated by ether- and acetone-soluble male extracts. This result, however, seems to occur only in one particular *S. mansoni* strain (Cardiff females) in which the vitelline cells of females can develop in the absence of males[75]. KUNZ et al. (1995)[52] proposed a hypothetical scheme in which the proliferation of the vitelline cells is controlled by an inductive signal acting as a mitogen, thus stimulating the mitotic proliferation of the vitellaria stem cells. The authors suggested a series of molecules participating in the signal transduction in *S. mansoni* as possible candidates mediating the process of vitelline cells proliferation.

Another line of thought, having ROBINSON (1960)[88] as its precursor, emphasizes the role of tactile stimulation in the sexual maturation of females. The importance of the tactile stimulus was shown in an interesting experiment carried out by POPIEL & BASCH (1984b)[77]. Males and females were cut into segments and paired in different arrangements and combinations. Unisexual females paired with small male fragments presented vitellogenesis, which, however, was limited to the region of contact.

An innovative hypothesis was raised by VOGEL in 1941[128] to explain the sexual development of females. This investigator proposed that the deficient muscle development of females may impair their nutrition and full somatic development. This approach emphasizing the importance of males in the process of nutrition of *Schistosoma mansoni* females was taken up again by GUPTA & BASCH (1987b)[41] and discussed in more detail in an interesting article later published by PAUL BASCH (1990)[7]. According to this investigator, the need for high reproductive efficiency has obliged present-day females to sacrifice some of their structural elements such as the pharyngeal and locomotor muscles. These losses have led to dependence on the male, whose well developed musculature may permit physical transportation as well as stimulation of growth by pumping blood inside females. The males may guarantee the survival of the species "not by donating sperm but by offering muscle". The growth and development of females may occur as the result of nutritional assistance "and not as a result of any mysterious growth factor emanating from the male".

Attributing female development simply to a chivalrous nutritional assistance on the part of males is a proposal that has stirred some controversy. According to SMITH & CHAPPEL (1990)[116], the sex reversal observed in paired males may be a sign of the existence of chemical messengers released to regulate development. Indeed, homosexual pairing between males has been observed in different schistosome species[2, 106, 129]. Well-developed males embracing small and sexually immature males is a phenomenon usually observed in this situation, except for *S. douthitti* whose males involved in homosexual pairing present the same size and sexual maturity[2, 106, 129]. On the basis of these observations it has been proposed that inhibition of the somatic and sexual development of males involved in homosexual pairing may be due to the same mechanism or pheromone responsible for the somatic and reproductive development of females[2, 129]. BASCH & GUPTA (1988)[9] did not detect the occurrence of female reproductive structures at the histological level. According to these investigators, the morphological alterations of "inner" males (stunted, with poorly developed testes) may be explained in nutritional terms; in this case, however, the male within the gynecophoral canal would have limited access to host blood.

Another aspect of the biology of schistosomes which is surrounded by a series of doubts has to do with the factors that guide the meeting of males and females in the vertebrate host. Evidence that worm pairing *in vitro* and *in vivo* seems to be chemically mediated has been obtained for several species of hermaphrodite trematodes[33, 34, 35]. For *S. mansoni* it has been proposed that components a human fecal lyophilized preparation have an attractive effect on mated worms[6]. On the basis of these assumptions, several studies were undertaken to detect the presence of chemical mediators responsible for the meeting of schistosomes. The data published in the literature are sometimes contradictory. IMPERIA et al. (1980)[48] consider the attraction between males and females to be chemically mediated, with males emitting pheromones that attract females. CHILDS et al. (1986)[17] proposed that males may be attracted by supernatant fluids from 72 hour cultures of female parasites. Documentation of the behavior of males and females in culture by means of time-lapse video tape photography showed that males respond more vigorously to females than females to males[95]. This attraction between worms occurs with and without barriers[32], and worms of the opposite sex, when separated, present predilection for mating with their original partner[103, 104]. MICHAELS (1969)[61] postulated the existence of highly differentiated receptors in both schistosome sexes, which may be responsible for mating and mating position. Attempts by the author to identify the class of compounds involved in attraction between males and females were unsuccessful.

The predominant view today is that if the meeting of males and females is chemically mediated the response to the stimulus must not be species-specific. On the basis of cross-mating studies in three systems, i.e., *Schistosoma mansoni* / *Schistosomatium douthitti* / *Heterobilharzia americana*[2], *Schistosoma haematobium* / *S. intercalatum*[118] and *Schistosoma bovis* / *S. curasoni*[90], it has been proposed that pairing may be processed in a fully random manner. ARMSTRONG (1965)[2] postulated more emphatically that pairing may result from thigmotaxis (by means of trial and error) rather than chemotaxis.

More recent results, however, support the idea of the existence of a "specific mate preference system"[124, 126].

Although the nature of the stimulus (physical or chemical) is a source of controversy, there is agreement that mating is a necessary requirement for maturation to occur[2, 7, 74] and for migration of the female to a definitive final site of residence in the vascular system of the vertebrate host[120]. It has also been proposed that the stimulus is not species-specific and, in some cases, not even genus-specific. Experimental interspecific[51, 59, 121] and intergeneric[8, 105] cross-infections have been obtained in which the females reach sexual maturity and produce viable eggs. There is also indirect evidence that hybridization may occur in nature between sympatric species[14, 55, 63, 73, 119, 134, 135]. True hybridization, however, must occur only between species belonging to the same group, i.e. phylogenetically very close species such as *Schistosoma mansoni* and *S. intercalatum*[121, 124]. The production of viable eggs in interspecific crosses involving less phylogenetically related species (*Schistosoma mansoni* and *S. haematobium*, for example) may be due to the phenomenon of parthenogenesis and not to true species hybridization[8, 51, 125].

Another aspect about which there seems to be some consensus is the difference and independent action between the stimulus for reproductive morphogenesis and the stimulus for somatic development. According to ARMSTRONG (1965)[2], sexual maturity may be a consequence of the tactile stimulus, whereas somatic maturity may depend on a specific substance such as a pheromone transferred via the tegument.

FINAL REMARKS

Despite a significant number of papers on the subject, the process or processes underlying the meeting of males and females in the circulatory system have not been determined and no consensus exists about the nature of the stimulus that triggers and maintains female development.

In the studies about their role, *Schistosoma* males have been considered, at times pejoratively, the sexual pair, the brother, the muscles or even the liver of females[7, 22, 85]. Indeed, we still must determine whether the stimulus responsible for female maturation involves the transfer of hormones, nutrients, neuromediators, mere tactile stimulation or a combination of chemotactic and thigmotactic factors.

What do males really do? This is almost a paradoxical way of closing a review about the sexual maturation of females. But all clues indicate that the secret rests there and this is definitely a question that should keep researchers busy for a few more years.

RESUMO

Determinação do sexo e desenvolvimento reprodutivo das fêmeas no gênero *Schistosoma*: uma revisão

Os parasitas do gênero *Schistosoma* situam-se entre os primeiros metazoários que desenvolveram sexos separados, determinado cromossomicamente no ovo fertilizado. Apesar da ocorrência de cromossomos sexuais específicos, as fêmeas de *Schistosoma* não atingem a maturidade somática e sexual sem a presença dos machos. Na verdade, um dos aspectos mais controversos e, ao mesmo tempo, mais fascinantes, envolvendo o desenvolvimento sexual das fêmeas está em se desvendar a natureza do estímulo que controla e mantém tal processo. Muito embora a natureza do estímulo (físico ou químico) seja motivo de controvérsia, concordam os mais diferentes autores que o acasalamento é um requisito indispensável para que ocorra a maturação e migração das fêmeas para o sítio definitivo de permanência no sistema vascular do hospedeiro vertebrado. Admite-se, ainda, que o estímulo não é espécie-específico e, em alguns casos, nem mesmo gênero-específico. Não obstante a existência de um número considerável de artigos dedicados ao tema, não há um consenso sobre o processo (ou processos) que controla(m) o encontro de machos e fêmeas no sistema circulatório do hospedeiro vertebrado, bem como está por ser determinada a natureza do estímulo, oriundo dos machos, que controla e mantém o desenvolvimento somático e sexual das fêmeas. Ao longo dos anos os machos de *Schistosoma* têm sido considerados, por vezes pejorativamente, os irmãos, os músculos ou o fígado das fêmeas. Em síntese, resta saber se a natureza do estímulo responsável pelo desenvolvimento das fêmas envolve a transferência de hormônios, nutrientes, a mera estimulação tátil ou a combinação de dois ou mais desses fatores.

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