REVIEW ARTICLE

The role of sex steroids in the complex physiology of the host-parasite relationship: the case of the larval cestode of *Taenia crassiceps*

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SUMMARY

Sex steroids play a significant role in regulating the parasite load in experimental intraperitoneal *Taenia crassiceps* cysticercosis of male and female Balbc/anN mice. Briefly, oestrogens increase parasite loads and androgens decrease them (1) by acting directly on the parasite, favouring or hindering its reproduction, respectively, and (2) by biasing the hosts' immune response towards a parasite-permissive Th2 or a parasite-restrictive Th1 response. The infected male host also undergoes drastic endocrinological and behavioural changes that may impinge upon the course of infection, and the host's mating behaviour and its exposure to predators. In addition, at different times of infection, significant changes occur in the expression of *c-fos* in the host's hyppocampus, hypothalamus and preoptic area. Thus, the host's brain seems to sense and/or react to intraperitoneal infection. The physiological domains of the network affected by the infection, which classically included the hypothalamus-pituitary-axis and the immune system, must now incorporate the host's sexual hormones and other areas of the brain. The network's complex circuitry and functions may help understand some basic questions of parasitology (i.e. the hosts' sexual dimorphism in parasite infections, host-parasite specificity, heterogeneity in the course and outcome of infections at different stages of parasite and host development). The plurality of elements and the complexity of the network that regulates the host-parasite relationship also point to additional strategies for the treatment and control of infections.

Key words: sex steroids, cysticercosis, *Taenia crassiceps*, host-parasite relationship.

INTRODUCTION

The role played by sexual dimorphism of the host in parasite infections of mammals is a matter of debate regarding its generality, causes, mechanisms and consequences. We maintain that sexual dimorphism does not favour the same sex in all host-parasite relationships, nor is it always mediated only by testosterone, nor necessarily does it transit through the host's immune system (Morales-Montor *et al.* 2004*a*).

We review here in some detail our extensive work on the role of sex steroids upon parasite growth of *Taenia crassiceps* metacestodes when injected into the peritoneal cavity of mice (mostly BalbC/AnN mice) and *in vitro*. Results argue for a complex network comprising the immune, endocrinological and nervous systems of both host and parasite in the regulation of the plural outcomes of infections, some favouring male hosts and other females.

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Facts indicative of sex-associated susceptibility to cysticercosis

The involvement of host sexual differences in cysticercosis first appeared in a Mexican national serological survey performed on a human open-population: women were more frequently seropositive and showed higher haemagglutination titres than men (Larralde *et al.* 1992). In *T. crassiceps* experimental murine cysticercosis, female mice were shown to consistently carry larger parasite loads than males, albeit to different extents (from 1·3 to more than 10 times), in the various inbred mouse strains tested (Sciutto *et al.* 1991). Greater numbers of cysticerci in naturally infected female rodents had been noted previously (Addis, 1946; Beck, 1951; Esch, 2004) and had prompted the use of females as the preferred host to experimentally propagate the parasite (Freeman, 1962; Dorais and Esch, 1969) but its significance and mechanisms had to be further explored. Sexual dimorphism merited consideration because of the large sex-associated differences in parasite loads, and because of their correlation with

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different levels of protection after vaccination (Sciutto *et al*. 1991).

Most studies use the BalbC/AnN inbred strain of laboratory mice as experimental host because it has proved to be the most favorable among several mouse strains for the parasite's establishment and reproduction. Intraperitoneal *T. crassiceps* cysticercosis of male and female BalbC/AnN mice (Freeman, 1962; Smith, Esch and Kuhn, 1972) lends itself well to controlled and reproducible experimentation, generating numerical data of parasite loads in individual mice in a matter of weeks after infection. Its general representation of other forms of cysticercosis was later strengthened by similar results in other mouse and parasite strains (Sciutto *et al*. 1991), by the parasite's extensive sharing of antigens with other taennids and cestodes and by the DNA homology of *T. crassiceps* with *T. solium* (Vega *et al*. 2003). Also, there is emerging evidence of sex bias in naturally acquired *T. solium* cysticercosis of pigs (Morales *et al*. 2002) and of humans (Fleury *et al*. 2004), in human schistosomiasis (Booth *et al*. 2004), in human leishmaniasis (I. Becker, personal communication), in echinococcosis (Barriga and Al-Khalidi, 1991) and other parasite infections of mammals (Aguilar-Delfin *et al*. 2001; Nacher *et al*. 2003).

MECHANISMS

The gonads and the thymus

Simple experimental approaches, like neonatal gonadectomy and thymectomy, and/or whole body irradiation of mice previous to cysticercosis infection, suggest that both the endocrine and immune systems are involved in the hosts' sexual differences of parasite loads, when measured 30 days after infection. Orchidectomy greatly increases parasite loads while ovariectomy reduces them (Huerta *et al*. 1992). Oestradiol and testosterone supplementation of gonadectomized mice restores their parasite loads to normal levels (Huerta *et al*. 1992; Terrazas *et al*. 1994). Thymus function seems to hinder parasite numbers in both sexes but more so in males than in females and, thus, sexual differences tend to disappear in thymectomized mice (Bojalil *et al*. 1993). Likewise, irradiation favours parasite growth in both male and female mice but more so in the male hosts (Huerta *et al*. 1992). T cell replenishment in thymectomized male and female mice, but not passively administred mouse whole immune sera, restores parasite loads and sexual differences in favour of females in association with restoration of cutaneous delayed hypersensitivity reactions (Bojalil *et al*. 1993). Vaccination is more effective in male mice than in female mice, both in reducing parasite loads and in increasing the number of mice totally free of parasites (Sciutto *et al*. 1990). Furthermore, a Th1 response is involved in resistance to infection, whereas Th2 activity associates with heavy parasite intensities, since mice that received anti-interleukin 10 (IL-10) Ab or recombinant IL-10 carried lower parasite intensities and developed a strong Th1-type response, while mice receiving anti-interferon gamma (IFN-γ) and anti-interleukin-2 (IL-2) Ab's, or recombinant IFN-γ or recombinant IL-2 showed a dramatic increase in susceptibility. Thus, the Th1-type immune response plays a fundamental role in protection against *Taenia crassiceps*, whereas Th2 does nothing, or may favour parasite establishment (Terrazas *et al*. 1999).

Together, the above findings prompt the hypothesis that sex steroids act upon parasite loads: oestradiol increases and testosterone limits parasite loads by mechanisms that possibly involve both the immune system of the host and the parasites reproductive system.

The endocrine-immune connection: do sex steroids control the host's immune response in cysticercosis?

The simplest hypothesis to connect the immune response with the females' greater parasite load is to propose that oestradiol directly favours a parasite-permissive Th2 immune response, which in turn down-regulates a parasite-hindering Th1 response. Thus, parasites grow immunologically undisturbed in a female endocrinological environment. The first premise is in keeping with the general notion that females produce more antibodies than males (Ahmed, Talal and Christadoss, 1987; Roberts *et al*. 2001) and the second refers to Th1/Th2 mutual downregulation (Mosmann and Coffman, 1989).

However, the numbers and types of lymphoid cells trafficking inside the infected peritoneal cavity do not show sexual differences in infected mice (Padilla *et al*. 2001), nor do the levels of circulating specific antibodies (Sciutto *et al*. 1990) or splenocyte proliferation and cytokine synthesis in response to *in vitro* antigen stimulation (Terrazas *et al*. 1998). The sera of infected mice of both sexes reflect a significant shift from Th1 to Th2 immune response during the course of infection. This is characterized by a marked decrease of IL-2 and IFN γ, enhancement of IL-6, IL-10 and IL-4 secretion (Terrazas *et al*. 1998; Toenjes *et al*. 1999; Rodríguez-Sosa *et al*. 2002). The shift starts in the first week of infection, when parasite reproduction rates are low, reaching an equilibrium in favour of Th2 at 4–6 weeks of infection, when parasites reproduce vigorously. However, the Th1/Th2 shift occurrs similarly in both male and female mice.

Thus, a major sex-associated immunological difference in antibodies or cytokines during infection that would account for the greater parasite loads in female mice could not be established.

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The immuno-endocrine connection: the role of the IL6 and P-450 aromatase

(*1*) *The inverse hypothesis*. Literature abounds on the numerous ways that sex steroids can influence immunologically active cells through their nuclear and membrane receptors to oestradiol, progesterone, prolactin, testosterone and other sex hormone metabolites (Arteaga, Chavarria and Morales-Montor, 2002). It is possible that sex steroids act behind the scenes of the most ostensible markers of immunity, enabling and disabling only the most specifically involved in controlling parasite growth. Can the immune system act upon the parasite by way of its effects on the endocrine system?

(*2*) *Immunological induction of host feminization*. Parasite loads of infected males reach the thousands during late infection and the relative sexual differences are minimized. Experiments designed to test an ensuing feminization process as the cause of the large paraite loads of chronically infected mice showed that infected male mice progressively became deandrogenized and oestrogenized (Larralde *et al*. 1995).

This rather startling finding of 'parasite-induced feminization of the host' is almost alone in the literature of parasite infections (Phillips and Cannon, 1978), especially in mammals (Lin *et al*. 1990; Isseroff *et al*. 1989) and has, inexplicably, attracted little attention.

(*3*) *The molecular mechanisms of feminization*. Feminization of chronically infected male mice logically follows from the IL-6's known capacity to induce the expression of P-450 aromatase (Reed *et al*. 1993). This enzyme's overexpression in the male host can shunt the metabolic pathway of testosterone towards dihydrotestosterone and switch it to oestradiol and, hence, feminization, TH1 inhibition and parasite replication. Fig. 1 depicts this hypothetical regulation network. Studies of changes in the infected mice mRNA levels for the enzymes involved in normal male steroid metabolism during infection reveals a decrease in the expression of 5α-reductase type II (the enzyme in charge of the conversion from testosterone to DHT) and an increase in the expression of P450-aromatase (responsible for the conversion of testosterone to oestradiol) (Morales-Montor *et al*. 1999). So, the shunt of testosterone to oestradiol is indeed turned-on in late infections and the metabolic pathway towards DHT is turned-off in chronically infected male mice. Feminization of the infected male has at least one plausible mechanism mediated by the immune system via Th2-dependent IL-6 (Fig. 1).

The suggestion that the immune system is indeed involved in feminization is supported by the finding that newly-irradiated or thymectomized male strain C57/Bl6 mice fail to feminize when chronically

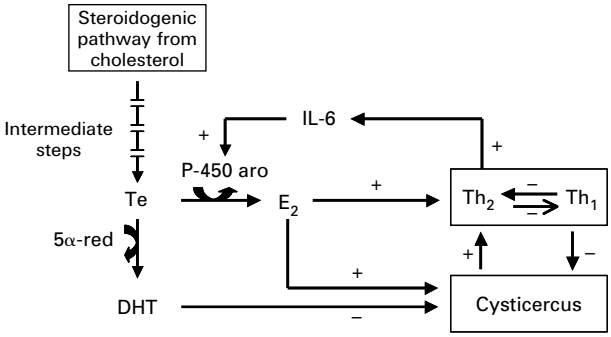

Fig. 1. Chart of the immunoendocrine mechanism of feminization in chronically infected male mice. The cysticercus antigenically stimulates the immune system: TH_2 cells produce IL-6 in addition to other molecules. IL-6 in turn, stimulates the expression of the enzyme P-450 aromatase, which aromatizes testosterone (Te) to oestradiol (E_2), instead of its conversion to dihydrotestosterone (DHT) by 5α-reductase. Thus, with time of infection, Th2 is progressively reinforced and Th1 is inhibited. In consequence, the infected male becomes feminized (oestrogenized and deandrogenized), favouring cysticercus reproduction because the high E_2 endocrine environment preferentially stimulates Th2 over Th1.

infected (Morales-Montor *et al*. 2001). The role the of IL-6 is further strengthened by the fact that IL-$6^{-/-}$ (KO) infected mice do not develop the feminization process, while the restitution with IL-6 restores feminization. Further involvement of IL-6 is documented by the testes-enhanced expression of the IL-6 gene. IL-6 has been shown to activate aromatase expression in the testes of cysticercotic mice and to induce active aromatization from androgens to oestrogens (Morales-Montor *et al*. 2001; Morales-Montor *et al*. 2002*a*, *b*, *c*). The increased serum levels of follicle-stimulating hormone (FSH) (the natural activator of aromatase expression, the secretion of which is also influenced by IL-6) detected in chronically infected mice, supports the notion that FSH interaction with IL-6 in the testes may cooperate in the induction of the feminization process (Morales-Montor *et al*. 2001).

(*4*) *Other immune participants*. Interleukin-6 and macrophage migration inhibitory factor (MIF) gene knockout (KO) mice of both sexes show that both male and female (*IL6*$^{-/-}$ and *MIF*$^{-/-}$) mice harbour similar numbers of parasites, with no changes in sex-hormone levels. However, the parental wild-type strains show the sex-associated differences in parasite loads, as well as the feminization of chronically infected male mice (Morales-Montor *et al*. 2002*c*). These results suggest that, besides IL-6, the MIF gene also plays a role in sex-associated differences of parasite loads in murine *T. crassiceps* cysticercosis.

(*5*) *Feminization may conceal innate sexual differences in immunity*. A significant consequence of feminization in chronic infection is that innate sex-associated differences in immunity and/or susceptibility

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may be concealed by the turning-on of aromatase in the male gonads as a response to infection. Distinct immunological differences between sexes would only be apparent if feminization of the infected male was prevented by blocking aromatase.

The possibility of immune concealment of sexual dimorphism was put to test by the administration of Fadrozole (a P450-aromatase inhibitor and hence suppressor of the production of 17β-oestradiol) to male mice before experimental infection (Morales-Montor *et al*. 2002*b*). Fadrozole treatment prevents oestrogenization and deandrogenization; it induces a 70% reduction in parasite loads and increases the splenocyte response to parasite antigens in relation to untreated feminized male mice. Interleukin-6 (IL-6) serum levels and its production by splenocytes are significantly augmented, together with an increase in its expression in the testes of untreated infected male mice. Fadrozole treatment returns these levels to baseline values (Morales-Montor *et al*. 2002*b*), implying that feminization does conceal the males more aggressive immunological control of the cysticercus.

Thus, IL-6 is a key molecule of the immune system that connects with the endocrine system through P450-ase, and it oestrogenizes and deandrogenizes the male hosts tending to equilize the parasite intensities and the immune profiles of infected male and female mice late in infection.

(*6*) *The involvement of thymus and spleen in feminization*. The question as to whether oestrogenization and deandrogenization affect the immunologically prominent thymus and spleen has been studied by mRNA expression patterns of *c-fos* and *c-jun*, two estradiol-regulated genes, as well as those of the *p53* and *bcl2* genes in the testes, spleen, and thymus of infected males. It was found that *c-fos* was significantly increased in all organs, *c-jun* was increased only in the thymus, *p53* mRNA was markedly reduced in all tissues, and *bcl2* was abolished only in the thymus (Morales-Montor *et al*. 1998). Thymic cell analysis performed by flow cytometry showed a reduction in the content of the CD3+, CD4+, and CD8+ subpopulations in the infected male mice. This finding suggests that the increase in oestradiol levels of the host could change the expression pattern of several genes that participate in the regulation of apoptosis in the thymus of male mice during chronic infection with *T. crassiceps* cysticerci, and that oestrogens may inhibit the cellular immune response to the parasite (Morales-Montor *et al*. 1998).

In an effort to identify the sex steroids involved in this gene scenario, the effects of testosterone, dihydrotestosterone, and 17β-estradiol in castrated mice of both sexes infected with *Taenia crassiceps* cysticerci were studied. Castration and treatment with either testosterone or dihydrotestosterone before infection markedly decreases parasite loads in both genders, while the treatment with 17β-oestradiol increases it in both genders. The specific splenocyte cell proliferation and IL-2 and IFN-γ production are depressed in infected-castrated mice of both genders, while treatment with testosterone or dihydrotestosterone produces significant cell proliferation recovery and enhanced production of IL-2 and IFN-γ. The opposite effect of the same sex steroids is found in the humoral response machinery: it is unaffected by testosterone or dihydrotestosterone restitution, while the treatment with oestradiol of both genders augmented the levels of anti-cysticercus IgG, and of IL-6 and IL-10 production. These results are congruent with the idea that androgens mediate immune functions which limit the cysticercus load, possibly through the stimulation of specific cellular immunity of the host (Morales-Montor *et al*. 2002*a*, *b*) (Fig. 2).

Direct action of sex steroids upon the cysticercus

Sex steroids can regulate parasite loads through their reciprocal interaction with immune mechanisms but, in addition, they can act directly upon the cysticercus reproductive system (Fig. 2). Oestradiol, and progesterone to a lesser extent, when added to *in vitro* cultures of *T. crassiceps* ORF strain, stimulate the parasite's production of buds, their DNA synthesis and [^{3} H]thymidine uptake, while testosterone and DHT are slightly inhibitory and even exert a pathogenic effect on the parasites (Escobedo *et al*. 2005). The possible molecular mechanisms by which sex-steroids affect *T. crassiceps* reproduction imply the presence in the parasite of hormone receptors, a totally unknown issue in cestodes. RT-PCR, and sequencing the specific amplified fragments, have shown the presence of oestradiol receptors (both α and β isoforms) and an androgen receptor, but not of progesterone receptors in the cysticerci of *T crassiceps*. Moreover, morphological studies of the parasite after sex-steroid treatment demonstrated that the E_2 and P_4-treated cysticerci are quite mobile, transparent, and surrounded by abundant buds. In contrast, T_4 and DHT-treated cysticerci are smaller than the E_2 or P_4-treated or than untreated cysticerci, and undergo progressive internal disorganization and develop opaque, whitish masses in their teguments, as well as showing progressive loss of motility. Furthermore, not only *in vitro* treatment of cysticerci affected their survival, but also pre-treatment of *T. crassiceps* with sex-steroids prior to their inoculation in male or female recipient mice had an effect on their infectivity: oestrogens promoted and androgens inhibited their infectivity. In contrast, prior exposure of parasites to T_4 and DHT significantly decreased the expected parasite load in male and female hosts (Escobedo *et al*. 2005). These last results are the first demonstration that sex steroids of

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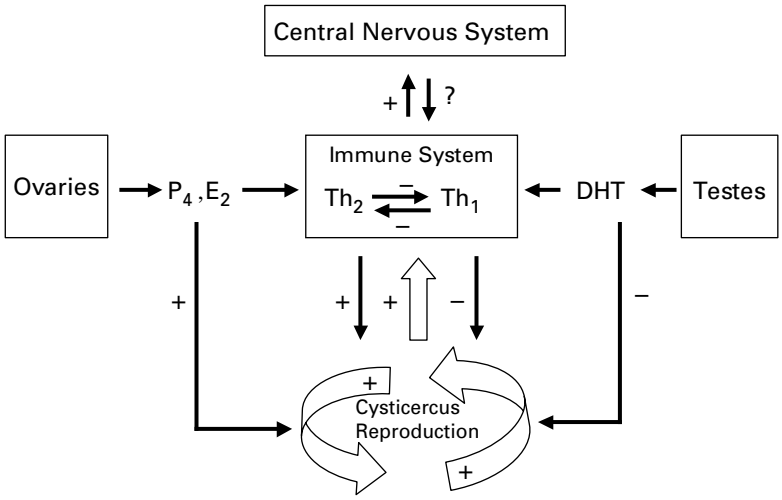

Fig. 2. Chart of the host-parasite neuroimmunoendocrine network in the control of cysticercus reproduction. Sex steroids may act directly upon the parasite whereby progesterone (P_4) and oestradiol (E_2) favour its reproduction, and dihydrotestosterone (DHT) inhibits it. Also, sex steroids act upon parasite loads via the immune system, E_2 favouring a permissive Th2 response that inhibits the restrictive Th1. The central nervous system (CNS) of the host shows changes that reveal that it senses and may react to the infection. The arrows show the interconnection among all system components. (+) Positive stimulation; (−) negative stimulation.

the host may act directly upon parasite reproduction by binding to classic and specific sex-steroid receptors on the parasite and stimulating their natural functions of controlling infectivity, differentiation, reproduction and apoptosis (Escobedo *et al*. 2005).

Furthermore, it has been shown that *T. crassiceps* cysticerci are able to metabolize sex-steroid precursors, and thus the parasites can make their own sex-steroids and are possibly sensitive to the host's regulators of hormonal expression (Gómez *et al*. 2000).

Hosts' behavioural changes in the infected host

The changes in hormonal host environment in male mice induced by *T. crassiceps* infection also affect other physiological aspects of the host, such as sexual (Morales *et al*. 1996), aggresive (Gourbal, Lacroix and Gabrion, 2002) and territorial behaviours (Gourbal *et al*. 2001). Male mice infected with *T. crassiceps* show remarkable changes in sexual behaviour: mounting, intromission, and ejaculation responses markedly decline as infection progresses. These sexual changes are characterized by a complete loss of the ejaculation response early at infection (6 weeks), followed by a gradual decrease in the number of mounts and intromissions, and their latencies were increased, until none of the parasitized mice showed any sexual response toward female mice (Morales *et al*. 1996). Moreover, changes in the sexual behaviour of infected male mice were associated with the serum levels of their sex-steroids, and testosterone or dihydrotestosterone restitution completely restored their normal sexual behaviour (Morales *et al*. 1996). Furthermore, experimental infection with *T. crassiceps* cysticerci disrupted the dominant-subordinate status (Gourbal *et al*. 2002). In infected male mice strong perturbations in territorial behaviour and aggressiveness are found. Infected dominant male mice do not show a significant reversal of dominance order compared to uninfected mice, and during the confrontation between naive infected and healthy mice, infected animals more often assume a subordinate status than healthy mice. The effects of infection by *T. crassiceps* were more likely to prevent adult male mice from becoming behaviourally dominant than to reverse existing dominance relationships (Gourbal *et al*. 2001, 2002).

THE INVOLVEMENT OF THE BRAIN IN MURINE CYSTICERCOSIS

Since *c-fos* is a key estradiol-regulated transcription factor gene involved in the regulation of sexual behaviour, it is possible that it changes its expression in the central nervous system (CNS) of infected male mice. Indeed *c-fos* expression showed significant oscillations with time of infection and to different magnitudes in hypothalamus, brain cortex and preoptic area but not in other areas of the brain or in several other organs of the host (Morales-Montor *et al*. 2004*b*). Significant changes in *c-fos* expression in the CNS during infection indicate that the brain senses the infection episode and may become involved in the ensuing behavioural changes of the infected mice. Through its extensive network of connections, the CNS may well extend the effects of infection to other physiological systems under its influence.

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Whether changes in the CNS are beneficial or not to the host or parasite remains speculative (Klein, 2000). One could argue that feminization of the male intermediate hosts favours the parasite by allowing reproduction in otherwise restrictive male mice, but equally arguable would be to consider feminization of the male host as deleterious to the parasite's completion of its cycle by reducing the male's exposure to its predators, the definitive hosts. Other similar mutually conflicting statements may be elaborated with the above premises, the true ones remain to be identified and could perhaps vary in each different host-parasite relationship.

CONCLUDING REMARKS

We have documented here that a complex interactive network involving the immune, endocrine and nervous systems of the mouse, as well as the reproductive system of the cysticerci, is in control of the parasite load of each infected mouse. If such a complex management of parasite loads (as that shown here between mice and cysticerci) extends to other parasite diseases of mammals (as current research seems to indicate in a number of infections) their means of exploration, understanding and forms of control must be reviewed and approached with designs matching in complexity and plasticity that of the physiology of infections.

Host and parasite sex-associated biases may be combined to favour their evolution towards a mutually acceptable relationship. Moreover, the changes in behaviour observed during cysticercosis, should not be regarded as simple biological curiosities but more as strong evidence of the plasticity of the host phenotype in response to infection by parasitic helminths. Furthermore, by changing the reproductive, aggressive and dominant capacity of the host, parasites generate novel questions regarding the evolution of host-parasite relationships in ways involving prey/predator interactions, stress, foraging, reproduction, and sexual selection (Zuk and Mc Kean, 1996).

In practical matters, the complexity of the host-parasite relationship suggests that all physiological factors (i.e. sex, age, developmental stage) should be taken into account in the design of vaccines and new drugs. Interventions aimed at the hormonal network appear as a possible new therapeutic approach to control murine cysticercosis in its intermediate host, and perhaps other infections.

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REFERENCES

Addis, C. J. Jr. (1946). Experiments on the relation between sex hormones and the growth of tapeworms. *Journal of Parasitology* **32**, 229–236.

Aguilar-Delfin, I., Homer, M. J., Wettstein, P. J. and Persing, D. H. (2001). Innate resistance to *Babesia* infection is influenced by genetic background and gender. *Infection and Immunity* **69**, 7955–7958.

Ahmed, S. A., Talal, N. and Christadoss, P. (1987). Genetic regulation of testosterone-induced immune suppression. *Cellular Immunology* **104**, 91–98.

Arteaga, M., Chavarria, A. and Morales-Montor, J. (2002). The immunoneuroendocrine communication network and the regulation of homeostasis: the use of hormones and neurohormones as immunotherapy. *Revista de Investigacion Clinica* **54**, 542–549.

Barriga, O. O. and Al-Khalidin, W. (1991). Effect of host sex and litter on the population dynamics of *Echinococcus granulosus* in dogs. *Journal of Parasitology* **77**, 927–930.

Bojalil, R., Terrazas, L. I., Govezensky, T., Sciutto, E. and Larralde, C. (1993). Thymus-related cellular immune mechanisms in sex associated resistance to experimental murine cysticercosis (*Taenia crassiceps*). *Journal of Parasitology* **78**, 471–476.

Beck, J. W. (1951). Effect of diet upon singly established *Hymenolepis diminuta* in rats. *Experimental Parasitology* **1**, 46–59.

Booth, M., Mwatha, J. K., Joseph, S., Jones, F. M., Kadzo, H., Ireri, E., Kazibwe, F., Kemijumbi, J., Kariuki, C., Kimani, G., Ouma, J. H., Kabatereine, N. B., Vennervald, B. J. and Dunne, D. W. (2004). Periportal fibrosis in human *Schistosoma mansoni* infection is associated with low IL-10, low IFN-γ, high TNF-α, or low RANTES, depending on age and gender. *Journal of Immunology* **172**, 1295–303.

Dorais, F. J. and Esch, G. W. (1969). Growth rates of two *Taenia crassiceps* strains. *Experimental Parasitology* **25**, 395–398.

Escobedo, G., Larralde, C., Chavarria, A., Cerbón, M. A. and Morales-Montor, J. (2005). Molecular mechanisms involved in the differential effects of sex-steroids on the reproduction and infectivity of *Taenia crassiceps*. *Journal of Parasitology* **90**, 1–10.

Esch, G. W. (2004). *Parasites, People and Places*. Cambridge University Press, Cambridge, UK.

Fleury, A., Dessein, A., Preux, P. M., Dumas, M., Tapia, G., Larralde, C. and Sciutto, E. (2004). Symptomatic human neurocysticercosis-age, sex and exposure factors relating with disease heterogeneity. *Journal of Neurology* **251**, 830–837.

Freeman, R. S. (1962). Studies on the biology of *Taenia crassiceps* (Zeder 1800) Rudolphi, 1810 (Cestoda). *Canadian Journal of Zoology* **40**, 969–990.

Gomez, Y., Valdez, R. A., Larralde, C. and Romano, M. C. (2000). Sex steroids and parasitism: *Taenia crassiceps* cisticercus metabolizes exogenous androstenedione to testosterone *in vitro*. *Journal of Steroid Biochemistry and Molecular Biology* **74**, 143–147.

Gourbal, B. E., Lacroix, A. and Gabrion, C. (2002). Behavioural dominance and *Taenia crassiceps* parasitism in BALB/c male mice. *Parasitology Research* **88**, 912–927.

Gourbal, B. E., Righi, M., Petit, G. and Gabrion, C. (2001). Parasite-altered host behavior in the face of a predator: manipulation or not? *Parasitology Research* **87**, 186–192.

Huerta, L., Terrazas, L. I., Sciutto, E. and Larralde, C. (1992). Immunological mediation of gonadal effects on experimental murine cysticercosis caused by *Taenia crassiceps* metacestodes. *Journal of Parasitology* **78**, 471–476.

Isseroff, H., Sylvester, P. W., Bessette, C. L., Jones, P. L., Fisher, W. G., Rynkowsky, T. and Gregor, K. T. (1989). Schistosomiasis: role of endogenous opioids in suppression of gonadal steroid secretion. *Comparative Biochemistry and Physiology* **94**, 41–45.

Klein, S. L. (2000). Hormones and mating system affect sex and species differences in immune function among vertebrates. *Behavioural Processes* **51**, 149–166.

Larralde, C., Padilla, A., Hernández, M., Govezensky, T., Sciutto, E., Gutierrez, G., Tapia-Conyer, R., Salvatierra, B. and Sepúlveda, J. (1992). Seroepidemiology of cysticercosis in Mexico. *Salud Publica de México* **34**, 197–210.

Larralde, C., Morales, J., Terrazas, I., Govezensky, T. and Romano, M. C. (1995). Sex hormone changes induced by the parasite lead to feminization of the male host in murine *Taenia crassiceps* cysticercosis. *Journal of Steroid Biochemistry and Molecular Biology* **52**, 575–581.

Lin, Y. C., Kikihisha, Y., Kono, H. and Gu, Y. (1990). Effects of larval tapeworm of (*Teania taeniformis*) on reproductive functions in male and female host rats. *Experimental Parasitology* **70**, 344–352.

Morales-Montor, J., Arrieta, I., Del Castillo, L. I., Rodriguez-Dorantes, M., Cerbon, M. A. and Larralde, C. (2004b). Remote sensing of intraperitoneal parasitism by the host's brain: regional changes of *c-fos* gene expression in the brain of feminized cysticercotic male mice. *Parasitology* **128**, 343–351.

Morales-Montor, J., Baig, S., Hallal-Calleros, C. and Damian, RT. (2002*a*). *Taenia crassiceps*: androgen reconstitution of the host leads to protection during cysticercosis. *Experimental Parasitology* **100**, 209–216.

Morales-Montor, J., Baig, S., Kabbani, A. and Damian, R. T. (2002*c*). Do interleukin-6 and macrophage-migration inhibitory factor play a role during sex-associated susceptibility in murine cysticercosis? *Parasitology Research* **88**, 901–914.

Morales-Montor, J., Baig, S., Mitchell, R., Deway, K., Hallal-Calleros, C. and Damian, R. T. (2001). Immunoendocrine interactions during chronic cysticercosis determine male mouse feminization: role of IL-6. *Journal of Immunology* **167**, 4527–4533.

Morales-Montor, J., Chavarria, A., De Leon, M. A., Del Castillo, L. I., Escobedo, E. G., Sánchez, E. N., Vargas, J. A., Hernandez-Flores, M., Romo-Gonzalez, T. and Larralde, C. (2004*a*). Host gender in parasitic infections of mammals: an evaluation of the female host supremacy paradigm. *Journal of Parasitology* **90**, 531–546.

Morales-Montor, J., Hallal-Calleros, C., Romano, M. and Damián, R. T. (2002*b*). Inhibition of P-450 aromatase prevents feminisation & induces protection during cysticercosis. *International Journal for Parasitology* **32**, 1379–1387.

Morales, J., Larralde, C., Arteaga, M., Govezensky, T., Romano, M. C. and Morali, G. (1996). Inhibition of sexual behavior in male mice infected with *Taenia crassiceps* cysticerci. *Journal of Parasitology* **82**, 689–693.

Morales-Montor, J., Rodriguez-Dorantes, M. and Cerbon, M. A. (1999). Modified expression of steroid 5α-reductase as well as aromatase, but not cholesterol side-chain cleavage enzyme, in the reproductive system of male mice during (*Taenia crassiceps*) cysticercosis. *Parasitology Research* **85**, 393–398.

Morales-Montor, J., Rodriguez-Dorantes, M., Mendoza-Rodriguez, C. A., Camacho-Arroyo, I. and Cerbon, M. A. (1998). Differential expression of the estrogen-regulated proto-oncogenes *c-fos*, *c-jun*, *bcl-2* and of the tumor-suppressor *p53* gene in the male mouse chronically infected with *Taenia crassiceps* cysticerci. *Parasitology Research* **84**, 616–622.

Morales, J., Velasco, T., Tovar, V., Fragoso, G., Fleury, A., Beltrán, C., Villalobos, N., Aluja, A., Rodarte, L. F., Sciutto, E. and Larralde, C. (2002). Castration and pregnancy of rural pigs significantly increase the prevalence of naturally acquired *Taenia solium* cysticercosis. *Veterinary Parasitology* **108**, 41–48.

Mosmann, T. R. and Coffman, R. L. (1989). TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annual Review of Immunology* **7**, 145–173.

Nacher, M., Singhasivanon, P., Treeprasertsuk, S., Silamchamroon, U., Phumratanaprapin, W., Fontanet, A. L. and Looareesuwan, S. (2003). Gender differences in the prevalences of human infection with intestinal helminths on the Thai-Burmese border. *Annals of Tropical Medical Parasitology* **97**, 433–435.

Padilla, A., Govezensky, T., Sciutto, E., Jimenez-Garcia, L. F., Gonsebatt, M. E., Ramirez, P. and Larralde, C. (2001). Kinetics and characterization of cellular responses in the peritoneal cavity of mice infected with *Taenia crassiceps*. *Journal of Parasitology* **87**, 591–599.

Phillips, W. J. and Cannon L. R. G. (1978). Ecological observations on the commercial sand crab *Portunus pelagicus* (L) and its parasite *Sacculina granifera* Boshma, 1973 (Cirripeda: *Rizocephala*). *Journal of Fish Diseases* **1**, 137–149.

Reed, M. J., Topping, L., Coldham, N. G., Purohit, A., Ghilchik, M. W. and James, V. H. T. (1993). Control of aromatase activity in breast cancer cells: the role of cytokines and growth factors. *Journal of Steroid Biochemistry and Molecular Biology* **44**, 589–593.

Roberts, C. W., Walker, A. H. and Alexander, J. (2001). Sex-associated hormones and immunity to protozoan parasites. *Clinical Microbiological Reviews*. **14**, 476–488.

Rodriguez-Sosa, M., David, J. R., Bojalil, R., Satoskar, A. R. and Terrazas LI. (2002). Cutting edge: susceptibility to the larval stage of the helminth parasite *Taenia crassiceps* is mediated by Th2 response induced via STAT6 signaling. *Journal of Immunology* **168**, 3135–3139.

Sciutto, E., Fragoso, G., Diaz, M. L., Valdez, F., Montoya, R. M., Govezensky, T., Lomeli, C. and Larralde, C. (1991). Murine *Taenia crassiceps*

cysticercosis: H-2 complex and sex influence on susceptibility. *Parasitology Research* **77**, 243–246.

Sciutto, E., Fragoso, G., Trueba, L., Lemus, D., Montoya, R. M., Diaz, M. L., Govezensky, T., Lomeli, C., Tapia, G. and Larralde, C. (1990). Cysticercosis vaccine: cross protecting immunity with *T. solium* antigens against experimental murine *T. crassiceps* cysticercosis. *Parasite Immunology* **12**, 687–696.

Smith, J. K., Esch, G. E. and Kuhn, R. E. (1972). Growth and development of larval *Taenia crassiceps* (cestoda). I. Aneuploidy in the anomalous ORF strain. *International Journal for Parasitology* **2**, 261–263.

Terrazas, L. I., Bojalil, R., Govezensky, T. and Larralde, C. (1998). Shift from an early protective TH1 immune response to a late permissive TH2-type response in murine cysticercosis (*Taenia crassiceps*). *Journal of Parasitology* **84**, 74–81.

Terrazas, L. I., Bojalil, R., Govezensky, T. and Larralde, C. (1994). A role for 17β-estradiol in immunoendocrine regulation of cysticercosis (*Taenia crassiceps*). *Journal of Parasitology* **80**, 563–568.

Terrazas, L. I., Cruz, M., Rodriguez-Sosa, M., Bojalil, R., Garcia-Tamayo, F. and Larralde, C. (1999). Th1-type cytokines improve resistance to murine cysticercosis caused by *Taenia crassiceps*. *Parasitology Research* **85**, 135–141.

Toenjes, S. A., Spolski, R. J., Mooney, K. A. and Kuhn, R. E. (1999). The systemic immune response of BALB/c mice infected with larval *Taenia crassiceps* is a mixed Th1/Th2-type response. *Parasitology* **118**, 623–633.

Vega, R., Pinero, D., Ramanankandrasana, B., Dumas, M., Bouteille, B., Fleury, A., Sciutto, E., Larralde, C. and Fragoso G. (2003). Population genetic structure of *Taenia solium* from Madagascar and Mexico: implications for clinical profile diversity and immunological technology. *International Journal for Parasitology* **33**, 1479–1485.

Zuk, M. and McKean, K. A. (1996). Sex differences in parasite infections: patterns and processes. *International Journal for Parasitology* **260**, 1009–1023.