Parasite regulation by host hormones: an old mechanism of host exploitation?

Galileo Escobedo¹, Craig W. Roberts², Julio C. Carrero¹ and Jorge Morales-Montor¹

¹Departamento de Inmunología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México AP 70228, Mexico City 04510, México
²Department of Immunology, Strathclyde Institute for Biomedical Sciences, University of Strathclyde, Glasgow, UK, G4 0NR

Recent experimental evidence suggests that parasites can not only evade immune responses actively but also exploit the hormonal microenvironment within the host to favor their establishment, growth and reproduction. The benefit for parasites of hormonal exploitation is so great that they have evolved structures similar to the steroid and protein hormone receptors expressed in upper vertebrates that can bind to the hormonal metabolites synthesized by the host. This strategy is exemplified by two parasites that respond to adrenal steroids and sexual steroids, respectively: Schistosoma mansoni and Taenia crassiceps. Understanding how the host endocrine system can, under certain circumstances, favor the establishment of a parasite, and characterizing the parasite hormone receptors that are involved might aid the design of hormonal analogs and drugs that affect the parasite exclusively.

Hormones and parasites

Hormones regulate a variety of cellular and physiological functions of organisms, such as growth, reproduction and differentiation [1,2]. Recently, the ability of hormones to affect the immunological response directed against pathogenic agents has gained attention [3–6]. This is evident during various parasitic diseases such as malaria, schistosomiasis, toxoplasmosis, cysticercosis, trypanosomiasis and leishmaniasis [7–11] in which strong hormonal regulation of the immune response has been described [12–17]. In Taenia crassiceps infection, the interaction of the immune and endocrine systems is dynamic and bidirectional (Box 1). However, factors other than the immunoenocrine system affect the course of a parasitic infection.

Parasites have developed diverse mechanisms of survival within the host that facilitate the establishment of infection. These mechanisms can be grouped into two types. The first is to evade the immune response by using strategies such as antigenic variation, molecular mimicry or affecting antigen processing and presentation [18–20]. For example, pathogens such as Chlamydia trachomatis and Coxiella burnetii have developed molecules that interfere directly with antigen processing and presentation [20]. In the second mechanism, the parasite exploits a host system to its benefit and, thus, obtains an advantage such as establishment, growth or reproduction [21]. For example, Naegleria fowleri can internalize antigen–antibody complexes from its surface. This mechanism provides the parasite with a dual benefit: first, obtaining amino acids for metabolism, and second preventing the surface-bound antibody from interfering with parasite–host-cell interactions [22]. A striking example of the exploitation of host molecules is the ability of several parasites to use host-synthesized cytokines as indirect growth factors for themselves [20,21].

Recent experimental evidence [23–32] has led us to propose a mechanism of host exploitation by parasites. In this system of ‘transregulation’, the parasite benefits directly from hormones or growth factors that are derived from the host to enable rapid establishment, and increased growth and reproduction rates. Transregulation has been described in at least eight parasitic infections that are caused by both protozoan and metazoans (Table 1).

Hormonal transregulation of parasite growth and reproduction

Adrenal hormones

It has been demonstrated that adrenal hormones exert a profound effect on several parasites. In vitro cortisol treatment of Plasmodium falciparum merozoites was found to increase the number and size of the gametocytes produced [31]. By contrast, when these parasites were treated with the dehydroepiandrosterone (DHEA) analog 16α-bromoepiandrosterone, growth rates diminished by 25% [27].

Cortisol was found to stimulate Entamoeba histolytica proliferation in a dose-dependent manner. By contrast, exposure of trophozoites to DHEA inhibited proliferation, reduced adherence and motility, and caused lysis in a dose-dependent manner. Consistent with this, cortisol increased, whereas DHEA decreased, levels of synthesis of parasite DNA (as determined by 3H-thymidine incorporation). Lysis of trophozoites by DHEA seems to be caused by a necrotic rather than apoptotic process, as determined through patterns of DNA fragmentation and enzymatic in situ labeling of apoptosis-induced DNA-strand breaks [detected by TdT-mediated dUTP–biotin nick-end labeling (TUNEL) assays]. A possible mechanism of action of trophozoite lysis by DHEA was suggested from

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Corresponding author: Morales-Montor, J. (jmontor66@biomedicas.unam.mx).

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Box 1. *Taenia crassiceps* causes feminization of male mice to alter immune function and facilitate reproduction

Female mice infected with *Taenia crassiceps* develop larger parasite loads than males in every inbred mouse strain that has been tested [48]. Gonadectomy, thymectomy and whole-body irradiation experiments demonstrate a role for both the endocrine and immune systems. Thus, orchidectomy in male mice lowers, whereas ovariectomy in female mice increases, parasite loads: effects that can be reversed by administration of testosterone or estradiol, respectively [48]. Gonadectomy is associated with reduced levels of splenocyte production of interleukin (IL)-2 and interferon (IFN)-γ, which can be restored by administration of androgen [50]. Thymectomy equalizes the number of parasites in both sexes [51]. Vaccination is more effective in male mice than in female mice, at both reducing parasite loads and increasing the number of parasite-free mice [52]. Despite these marked differences between the genders, parasite loads in males increase with time compared with those of females. This is because of parasite-mediated deandrogenization and estrogenization of male mice [11]. These processes are associated with tissue damage in the male reproductive system [53] and with specific changes in mRNA levels for the enzymes that are involved in normal male steroid metabolism: a decrease in the expression levels of 5α-reductase type II and an increase in the expression levels of P450 aromatase [54]. This is accompanied by a reduction in numbers of thymic CD3⁺, CD4⁺ and CD8⁺ subpopulations, suggesting a role for estradiol in inhibition of the cellular immune response to *T. crassiceps* [55]. Total irradiation or neonatal thymectomy prevents these changes in the levels of serum steroids in chronically infected male mice, indicating a role for the immune system [56]. Of note, IL-6⁺ gene-knockout mice infected with *T. crassiceps* do not undergo feminization, whereas restitution with recombinant IL-6 enables feminization. Thus, IL-6 activates aromatase expression in the testes of cysticercotic mice and causes active aromatization from androgens to estrogens. Administration of an inhibitor of estradiol production (fadrozole) can reduce parasite loads by up to 70% in both sexes of infected mice. This is associated with recovery of the specific cellular immune response, and augmentation of serum IL-6 levels and expression in the testes of infected male mice. Treatment with progesterone and the subsequent metabolism of this hormone to estradiol increase parasite loads in both genders of infected mice, possibly through manipulation of the specific cellular immune response of the infected host [57].

Table 1. Direct effects and possible molecular mechanisms of host hormones on parasite physiology

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Hormone</th>
<th>Parasite life-cycle phase</th>
<th>Effects</th>
<th>Molecular mechanism</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Plasmodium falciparum</em></td>
<td>Cortisol, E₂, P₄, T₄, insulin</td>
<td>Merozoites</td>
<td>↑Growth, ↑reproduction</td>
<td>Unknown</td>
<td>[29,31]</td>
</tr>
<tr>
<td></td>
<td>16α-α-Bromoepeandrosterone</td>
<td>Merozoites</td>
<td>↓Growth</td>
<td>Unknown</td>
<td>[27]</td>
</tr>
<tr>
<td><em>Schistosoma mansoni</em></td>
<td>Cortisol, DHEA</td>
<td>Cercariae, schistosomula, adult worms (both sexes and paired)</td>
<td>↓Reproduction, ↓viability, ↓oviposition</td>
<td>Binds to classical nuclear receptor and inhibits glucose metabolism</td>
<td>[37]</td>
</tr>
<tr>
<td><em>Schistosoma haematobia</em></td>
<td>T₄</td>
<td>Cercariae</td>
<td>↓Reproduction</td>
<td>Inhibits SmNDS and its mitochondrial function</td>
<td>[24]</td>
</tr>
<tr>
<td><em>Trypanosoma cruzi</em></td>
<td>EGF</td>
<td>Amastigotes</td>
<td>↑Growth, ↑reproduction, ↑metabolic activity</td>
<td>Activates PKC and MAPK pathways</td>
<td>[23]</td>
</tr>
<tr>
<td><em>Brugia malayi</em></td>
<td>EGF</td>
<td>Microfilariae</td>
<td>↑Growth, ↑differentiation</td>
<td>Increases transcription levels of Raf and Ran</td>
<td>[26]</td>
</tr>
<tr>
<td><em>Onchocerca volvulus, Onchocerca lienalis</em></td>
<td>Hydroxyecdysone</td>
<td>Microfilariae</td>
<td>↑Metabolic activity</td>
<td>Binds to parasite classical nuclear receptor and regulates transcription</td>
<td>[28,41–43]</td>
</tr>
<tr>
<td><em>Leishmania mexicana</em></td>
<td>GM-CSF</td>
<td>Promastigotes</td>
<td>↑Growth</td>
<td>Direct stimulation by unknown mechanism</td>
<td>[30]</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
<td>Cortisol</td>
<td>Trophozoites</td>
<td>↑Reproduction, ↑metabolic activity</td>
<td>Unknown</td>
<td>[33]</td>
</tr>
<tr>
<td></td>
<td>DHEA</td>
<td>Trophozoites</td>
<td>↓Reproduction, ↓viability, ↓infecitvity, ↓metabolic activity</td>
<td>Inhibits 3-hydroxy-3-methyl glutaryl CoA reductase</td>
<td>[33]</td>
</tr>
<tr>
<td><em>Taenia crassiceps</em></td>
<td>E₂, P₄</td>
<td>Cysticerci</td>
<td>↑Growth, ↑reproduction, ↑viability, ↑infecitvity</td>
<td>Steroid binds to its specific receptor and activates c-Fos and c-Jun transcription</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>T₄, DHT</td>
<td>Cysticerci</td>
<td>↓Growth, ↓reproduction, ↓viability, ↓infecitvity</td>
<td>Steroid binds to its specific receptor and inhibits c-Fos and c-Jun transcription</td>
<td>[32]</td>
</tr>
</tbody>
</table>

*Abbreviations: E₂, estradiol; P₄, progesterone; T₄, testosterone.*
schistosomiasis and, in fact, is as effective as the most effective vaccine antigen candidates [36]. Also, cortisol and DHEA inhibit oviposition by *S. mansoni* both *in vitro* and *in vivo* [37]. *In vitro*, DHEA has strong cercaricidal and schistosomulicidal effects, in addition to decreasing adult worm survival rates by up to 100% [37]. It has also been demonstrated that adrenal function alters with age during primary and secondary *S. mansoni* infection in baboons [38,39] and mice [38], and this change correlates with the intensity and type of infection [38]. Moreover, adrenalectomized infected mice displayed increased mortality rates and numbers of adult worms, and twice as many ova per worm pair in their liver [40]. Thus, the evidence suggests that a lack of adrenal steroids, particularly DHEA, mediates an increment of the adult worm burden and promotes worm fecundity *in vivo* and *in vitro*.

**Sex- and pregnancy-associated hormones**

Treatment of adult *Schistosoma haematobium* with testosterone diminishes fertility and, thus, the reproductive capacity of this parasite [24]. Treatment of *T. crassiceps* cysticerci with 17-β-estradiol increases their reproductive capacity by increasing the number of buds, whereas treatment with testosterone or dihydrotestosterone (DHT) diminishes this function. In addition, viability, growth and infective capacity of cysticerci are increased to 200% after treatment with estrogen but are inhibited almost completely by androgen treatment [32]. In separate studies, treatment of *P. falciparum* merozoites with estradiol, progesterone or testosterone increased the number of gametocytes that were produced *in vitro* [29].

It has been shown that the *in vitro* exposure of *E. histolytica* trophozoites to several concentrations of sex steroids such as 17-β-estradiol, progesterone, testosterone and DHT has little effect on parasite viability or proliferation [33].

**Other host-derived factors**

*Trypanosoma cruzi* amastigotes that are treated *in vitro* with murine epidermal growth factor (EGF) increase their levels of DNA synthesis, growth and metabolic activity considerably [inducing receptors with tyrosine kinase, protein kinase C (PKC) and mitogen-activated protein kinase (MAPK) activity] [23]. Treatment of *P. falciparum* merozoites with insulin increases the number of gametocytes produced *in vitro*. Similarly, murine EGF stimulates the *in vitro* development and maturation of *Brugia malayi* microfilariae and other filarial parasites [26]. It has also been demonstrated that *Onchocerca volvulus* and *Onchocerca lienalis* microfilariae increase their metabolic activity when treated *in vitro* with 20-hydroxyecdysone [28]. Granulocyte–macrophage-colony-stimulating factor (GM-CSF) augments the *in vitro* growth of *Leishmania mexicana* promastigotes [30].

**Transregulation of parasite signal-transduction pathways**

**Regulation of gene expression**

The mechanisms by which host hormones act on parasites have recently been investigated, and some parasite molecules that are involved in transregulation have been identified and characterized [32,41]. These include receptors, transporters, steroidogenic pathway enzymes and second messengers that are synthesized by parasites and that enable the exploitation of host hormones. Several lines of investigation are in progress to determine whether

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**Figure 1.** Host steroid hormones can affect several aspects of parasite physiology. Steroids (e.g. estradiol, testosterone, progesterone, DHEA and cortisol) from the host can bind to specific cytoplasmic receptors that are expressed by the parasite. The ligand–receptor complex can regulate, through genomic mechanisms, parasite growth, infectivity, differentiation and reproduction. The ability of the parasite to bind to host molecules and use them to its own benefit is mediated by a mechanism that we have denominated transregulation. Abbreviations: HRE, hormone response element; SH, steroid hormone; SHR, steroid hormone nuclear receptor.

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classical nuclear receptors can be found in parasites and, if so, whether they can bind to host hormones to direct downstream transcriptional events (Figure 1).

Sani et al. [41] characterized ‘specific retinol and retinoic acid-binding proteins’ in *O. volvulus*, *Onchocerca gibsoni*, *Dipetalonema viteae*, *Brugia pahangi* and *Dirufilaria immitis*. The role ascribed to these proteins was that of binding to host hormones and mediating the biological effects of retinoids on parasites, such as growth, reproduction and differentiation. The genome of *O. volvulus* codes for at least three classical nuclear receptors [42]; two of these (OvNR-1 and OvNR-2) have been characterized and found to be similar to the retinoid receptors in vertebrates and to the *Drosophila melanogaster* protein EiP78c. Computer modeling suggests that these molecules possess a ligand-binding cavity that is of a size and form capable of binding to a steroid [42,43].

The presence of receptors in *S. mansoni* that can bind to 17-β-estradiol provides a likely mechanism for the protective effect of this hormone in infected mice and hamsters [44]. In the same parasite, classical nuclear receptors for steroids, thyroid hormones and ecdysteroids have been characterized [45]. Homology among these receptors and those described in *Drosophila*, mice and humans ranges from 70% to 95%, hence their enormous capacity to bind to host hormones and affect diverse developmental processes of *Schistosoma* spp. [45]. It has been shown that cysticerci of the helminth parasite *T. crassiceps* express an androgen-receptor-like mRNA and both isoforms of the classic estrogen receptor (α and β), but there is no expression of either isoform (A or B) of progesterone receptors [32]. It seems that the direct *in vitro* effects of estrogens and androgens on *T. crassiceps* reproduction are due to the binding of estradiol and testosterone to their respective receptors. The small effects of progesterone observed in the apparent absence of its specific receptor could be due to non-conventional nuclear receptors or could reflect the transformation of this hormone to estradiol, as shown for androgens [46].

Binding of the estrogen receptor to classic estrogen-dependent elements could be responsible for the activation of activator protein (AP)-1 complex genes in the normal metabolism of *T. crassiceps* [32].

**Regulation of protein phosphorylation**

Rapid-action or non-genomic mechanisms have been investigated more prolifically than those involving the presence of a classical nuclear receptor (Figure 2). However, this apparent advantage is only relative because the first reports indicating that host hormones might activate cascades of second messengers appeared only at the beginning of this century [23,26]. EGF is a molecule that can activate different signaling pathways in parasites and that has been amply studied [23]. The presence of a complete signaling cascade that corresponds to the Raf kinases has been determined in *B. malayi* [26]. Murine EGF increases transcription levels of Raf kinase and Ran – a nuclear GTPase in *B. malayi* – and has been demonstrated to promote phosphorylation of some microfilarial proteins. Moreover, physical interaction increases between Ran and other proteins (which are yet to be defined) and promotes phosphorylation of some proteins of microfilarial origin. By contrast, *T. cruzi* amastigotes synthesize a receptor that can bind to human EGF to induce the activity of parasite MAPK and PKC cascades in a dose- and time-dependent manner. As proposed by

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**Figure 2.** An alternative mechanism of parasite exploitation of the hormonal environment in an immunocompetent host. This mechanism does not involve the binding of hormones to classical nuclear receptors but, instead, the capability of parasites to bind hormones to their cell membrane and activate downstream signal-transduction pathways. The ligand–receptor complex can regulate – through activation of specific signal-transduction cascades such as those involving inositol (1,4,5)-trisphosphate (IP3), PKC, extracellular-signal-regulated kinases (ERKs) and MAPK – vital processes of parasite physiology, including growth, infectivity, differentiation and reproduction. Abbreviations: DAG, diacylglycerol; EGFR, EGF receptor; IP3, IP3 receptor; JNK, N-terminal c-Jun kinase; NF-ATp, nuclear factor of activated T cells; PLC, phospholipase C; PR, progesterone receptor; RTK, receptor tyrosine kinase.
Ghansah et al. [23], these results suggest the existence of a mechanism that regulates growth and parasite proliferation through a signaling pathway that is dependent on human EGF. Similarly, the presence in S. mansoni of a receptor (SmRTK-1) with a high degree of structural homology to the insulin receptor catalytic domains has been determined. Preferential localization of SmRTK-1 in sporocysts and oocytes could favor differentiation and growth processes in this parasite [47] because receptors with tyrosine kinase activity typically control aspects of metabolism, growth and development. Recent studies show that S. haematobium synthesizes a 28-kDa protein, Sh28GST (S. haematobium glutathione-S-transferase of 28 kDa), that can bind to testosterone and facilitate the transport, metabolism and physiological action of this hormone in the parasite [24].

Concluding remarks

In light of this evidence, it is clear that the host endocrine system can not only influence the course of parasitic infection by modulating the immune system but also be exploited directly by parasites. Thus, by means of genomic (Figure 1) and non-genomic (Figure 2) mechanisms, host hormones regulate important parasite processes such as growth, differentiation and reproduction through a mechanism described as transregulation. In some cases, this mechanism enables the parasite to accomplish a more successful infection. In other cases, transregulation might benefit the host by reducing the success of parasite infection.

Comprehension of the concepts of transregulation and host exploitation, in addition to the study of classic nuclear receptors and receptors that regulate the activity of various second-messenger cascades in parasites, provides interesting research perspectives in the complex host–parasite evolutionary relationship. Nuclear receptors in parasites are scarce and have been described in only six parasites to date. However, as more parasite genome projects reach completion, evidence of these receptors in other parasites is likely to accumulate. Recent evidence that cysticerci of T. crassiceps possess 17-β-hydroxy steroids dehydrogenase activity that can metabolize androstenedione to testosterone [46] suggests that steroid hormones will also be identified, at least in eukaryotic parasites.

The ability of a parasite to affect a female or male host of the same species differentially (sexual dimorphism of an infection) can be mediated by hormonal regulation of the immune response of the host or by direct hormonal effects on the parasite. Understanding the contribution of each of these effects and the characterization of the parasite molecules involved might facilitate the development of drugs that counteract the effects of hormones on the host immune system or the parasite.

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