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Impact of Parasitic Infection on Immune Responses and Reproductive Outcome

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Abstract: The parasite infection is responsible for major economic losses in agriculture throughout temperate regions of the globe. Control measures are heavily reliant on chemotherapy resulting in the emergence of drug resistant parasite populations. Control strategies needs deeper knowledge of host-parasite interactions. Herein we discuss recent advances in the understanding of the immune response to different parasites and its impact on reproductive performance, integration of cytokine bias due to pregnancy and due to infection with better understanding to antigen/pathogen clearance mechanisms, Co-stimulatory signals, Antigen presenting cell type, Cytokine environment during initial antigenic exposure,. Understanding immune evasion strategies of pathogen/parasite will be crucial for future research into parasite control measures and defining points at which redirection is possible.

Key words: Parasites-host/ parasite interactions · Immune response · Reproductive performance

INTRODUCTION

Currently, the incidence of infertility becomes relatively increased with consequent reduction of productivity of farm animals [1]. Parasites are a major cause of productivity losses and morbidity in livestock worldwide as they infect a quarter of the total world's animal population [2,3]. Regarding the impact of parasitism on reproduction, pathogenic protozoa were found to be associated with severe genital lesions, temporary or permanent anestrus and abnormal estrous cycles, delayed puberty, cystic ovaries and endometritis in livestock [4, 5]. Moreover, infection during pregnancy may lead to premature births, prenatal losses, retained placenta, low offspring birth weight and delayed onset of postpartum ovarian activity in Boron cattle [6].

During evolution parasites have developed various mechanisms for the successful invasion and persistence in their hosts: camouflage by acquisition of host derived molecules, molecular mimicry by synthesizing structures related or identical to host biomolecules or immunomodulation by active interference with the hosts' immune reactions [7].

This work explored the plasticity of immune responses and the delicate balance between health and disease, using examples from immunoparasitology and reproductive biology.

Cytokine Bias and Immune Outcomes: More than two decades ago, it was recognized that depending on the stimuli used to activate and maintain lymphocytes *in vitro*, the type of cytokines produced differ markedly [8]. Some clones of CD4+ T cells functionally defined as helper T (Th) cells, when maintained *in vitro* for extended periods, express well-defined patterns of cytokines. Some cells differentially express either IL-2, interferon (IFN)-γ and TNF-α (Th1) or IL-4, IL-5, IL-6, IL-10 and IL-13 (Th2). In recognition that CD8+ T cells, natural killer (NK) cells, NK-like T (NK T) cells, mast cells and other myeloid leukocytes, also secrete 'Th1' and 'Th2' cytokines, these groupings are now more appropriately described as Type 1 and 2, immune response. By activating macrophages (IFN-γ) and neutrophils (TNF-α), Type 1 cytokines are valuable in controlling intracellular pathogens and in allograft rejection. Type 2 cytokines down-regulate macrophage activity (IL-4), promote B lymphocyte

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activation (IL-4 and IL-5) and the synthesis of IgG1 and IgE (IL-4) and drive mast cell (IL-4) and eosinophil (IL-5) production. Type 2 cytokines have been associated with resistance to some species of helminths and with reproductive success, but also with adverse outcomes in allergy, asthma and immunity to protozoan parasites [9].

Of special interest is the potential for some cytokines to enhance production of either Type 1 or 2 cytokines (IFN-γ and IL-12 or IL-4 and IL-13, respectively). This positive feedback and also cross-inhibition in cytokine production, provide mechanisms for the development of the highly directed immune responses.

It should also be understood that although highly biased or polarized cytokine expression patterns may be seen in some diseases and experimental models, mixed cytokine responses will be normal and are necessary in most circumstances. For example, even where polarized Type 1 immune responses are known to be protective (e.g. during chronic infections with intracellular protozoan pathogens),T cells secreting both Type 1 (IFN- γ) and Type 2 (IL-10) cytokines appear to be essential in preventing immunopathology [11].

Immune Regulation for Successful Pregnancy: Eutherian (placental) mammals presents a theoretical challenge to the self-non self model of immune activation. It is supposed that the maternal immune system should reject a fetus that has inherited half of its genes from its father, a prediction that does not hold up. Several explanations was reported for maternal acceptance of the semi-allogeneic fetus, among which, was the suppression of the maternal immune system [10]. However, if this was the case, a logical consequence would be increased maternal susceptibility to infections and tumors during pregnancy, a phenomenon that is not generally observed. This dichotomy has been resolved to a certain extent by the observation there is regulated modulation, rather than suppression, of the maternal immune system [11, 12].

We must first look at cytokine production in the placenta during normal pregnancy where certain cytokines in the placenta are beneficial during pregnancy while others are detrimental. Among those that appear beneficial are colony stimulating factor one (CSF-1), transforming growth factor beta (TGF-β), granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-10(IL-10). Whereas CSF-1 is necessary for implantation [13]. TGF-β can inhibit trophoblast invasion and therefore protect the mother, with the additional potential of inhibiting NK cell activity [14]. GM-CSF has anti-apoptotic properties and may therefore function by promoting trophoblast survival [15]. IL-10 has an anti-inflammatory effect that is necessary for implanatation. Among those cytokines that appear to be detrimental are TNF-α, IFN-γ and IL-2, which are usually expressed at very low levels or are absent in normal placenta. TNF-α can cause thrombosis and smooth muscle contraction. It is secreted by macrophage to activate the NK cells that produce IFN-γ, which further activated the macrophage to produce more TNF- α untile the activated NK cells killed the embryo [16]. The production of TNF- α in the deciduas is associated with abortion while the production of TGF-β by γ T cells later in pregnancy was beneficial.

Some cytokines may have both beneficial and detrimental effect depending on concentration or stage of pregnancy. Thus, IFN-γ has been shown, conflictingly, to be essential for maintenance of pregnancy [17] and to do abortifacient [18] in later pregnancy.

It was concluded that the major feature of maternal immune modulation should be the bias towards a Th (helper)-2 type phenotype away from a Th1-type phenotype, characterized by an increased ratio of IL-4 relative to IFN-γ production. The Th1/Th2 paradigm in pregnancy has been re-evaluated and it is now considered to be an over-simplification of maternal immune modulation [19]. Furthermore, a role for regulatory T cells (Th3/Treg) in normal pregnancy has been identified recently, adding to the complexity of cytokine interactions in the maternal periphery [20]. Nevertheless, it is still recognized that alterations in cytokine production do occur during normal pregnancy, with a predominance of IL- 4 [21].

What Are the Underlying Mechanisms That Influence the Maternal Immune Response?: The answer may lie in the physiological signals essential for the maintenance of pregnancy, namely hormones. Maternally-and fetally-produced hormones such as progesterone, estrogen and prostaglandins are fundamental in supporting the pregnancy from implantation to its successful outcome. The immunomodulatory effects of pregnancy-related hormones are multi-fold. Progesterone is of particular interest with regards to cytokine profiles since it is known to induce IL-4 production by Th2 cells and inhibit the cytotoxic activities of T cells (CD8+T) and NK cells [22]. 17β-Oestradiol enhances both IL-10 and IFN-γ secretion by antigen-stimulated T-cell clones. These apparently contradictory effects are dose-related phenomena. This may account for a regulatory or Th2-type cytokine bias during pregnancy and also for the increased reactivity observed in non pregnant females [23].

In the same time, the trophoblast secretes interferon tau (IFN-γ) and both trophoblast and endometrium secrete prostaglandin E2 (PGE_2) and the endometrial glands secrete serpins (uterine milk proteins), all of which inhibit lymphocyte activation to keep on the embryo not rejected by the dam and help in implantation. PGE_2 is known to bias the cytokine profiles of dendritic cells towards IL-10 production, reducing IL-12 production; the lack of IL-12 production by these dendritic cells results in the development of T cells producing high concentrations of IL-4 and IL-5 upon priming [24]. Collectively, these data point to modulation towards an anti-inflammatory cytokine phenotype during pregnancy. Furthermore, non-classical, class I MHC antigens expressed by trophoblasts prevent maternal NK-mediated cytotoxic responses [23].

Towards the end of pregnancy course placental separation occurs when fetal cortisol induces the production of the enzymes 17α hydroxylase and aromatase in the placenta which favour oestrogen synthesis at the expense of progesterone synthesis. Maternal plasma levels of oestradiol 17β increase suddenly, while plasma levels of progesterone decline sharply immediately prior to parturition.

Spontaneous myometrial contractility is augmented by autocrine and paracrine release of $Pgf_{2\alpha}$ and parturition ensues. Disturbed endocrine function, high progesterone and cortisol level and low estradiol level was traced in cows blood with retained placenta [20]. Also, at the time of parturition, maternal immunological recognition of fetal MHC class I proteins expressed by trophoblast cells triggers an immune/inflammatory response and activation of cytotoxic T cells (CD8+T) and NK cells that contributes to placental separation [25]. This lymphocytic activation was suppressed at the foeto maternal interface alongside the pregnancy course to avoid rejection of fetal allograft [26].

Chemotactic factor for leukocytes is found in placentomes of cows with normal placental separation. While, a strong impairment in polymorphonuclear neutrophiles chemotaxis was demonstrated in placentomes from cows with retained placenta [27].

Cytokine Bias after Infections with Protozoan Parasites: Much consideration has been given to how biased cytokine responses might develop. Obviously there may be great therapeutic benefits from understanding the plasticity of immune responses and defining points at which redirection is possible. The cytokine environment induced at the time of introduction of antigen is a major factor in determining the direction in which an immune response will develop. These cytokines might originate from infected or otherwise activated somatic cells and from leukocytes recruited to the site of infection or antigen challenge. Also, there are some factors influencing the immune response such as, the type and dose of antigen, the route of delivery, Persistence, Efficiency of antigen/pathogen clearance mechanisms, Co-stimulatory signals, Antigen presenting cell type, Cytokine environment during initial antigenic exposure, Regulatory regions of cytokine genes, Intracellular signalling pathways, Recipient or host MHC haplotypes and Immune evasion strategies of pathogen/parasite.

Leishmania Major: Several protozoan parasites, including Plasmodium, Toxoplasma and Leishmania are known to compromise pregnancy [28]. It has been reported that the Th1 response associated with protozoan parasite infections compromises the viability of the foetus, whereas a Th2 response aids the maintenance of pregnancy, but may allow parasite transmission to the foetus and compromise the health of the mother by increasing parasite burden. Despite the *L.major* infection is peripheral and the organism does not invade the placenta, It affects on the outcome of pregnancy and in the same time, pregnancy influence the quality of the maternal immune response against the infection. Protection against *L. major* infection is associated with the ability of the host to generate a Th1-type inflammatory response whereas susceptibility is associated with a Th2-type anti-inflammatory response. Therefore, IFN-γ is curative whereas IL-4 is not. Pregnancy may lead to larger cutaneous lesions and harbouring more parasites [29]. However, infected mice also exhibits an increased number of fetal resorbtion attributed to IFN-γ production in response to infection [30] and this support the hypothesis that Th1-type immune reactivity is detrimental to pregnancy.

Toxoplasma Gondii: Studies of this parasite have suggested that Th1 response due to infection compromises the viability of the foetus, which requires a localised Th2 response for survival. The Th1 response can also be modified by the presence of Th2 cytokines during pregnancy, resulting in an increase in parasite burden and transmission of the parasite to the foetus [28]. The production of the Th1 inhibitor IL-10 is a mechanism used by the immune system to reduce the production of toxic levels of inflammatory cytokines. This protective mechanism has been demonstrated in a model of *T. gondii*

infection, in which IL-10-deficient mice died as a result of overproduction of IL-12, IFNγ and TNFα, which was associated with host pathology [26]. Pregnant IL-4-deficient mice show a decrease in transmission of *T. gondii* to the foetus, when compared to pregnant wild-type mice [31]. A common feature of these parasite infections is the Th1-biased immune response exhibited by the host in response to infection by these organisms [32].

T. gondii adverse effect on pregnancy, depends on the timing of infection relative to gestation. Thus, chronically infected pregnant humans, sheep or mice harbouring tissue cysts generally do not transmit parasites congenitally nor suffer any ill effects themselves [33]. The exception to this appears to be in chronically infected outbreed and field mice, which can transmit parasites congenitally [31]. However, if infection occurs in the first trimester, the risk of abortion is relatively high, although transmission of parasites to the foetus is low. By contrast, if infection occurs during the third trimester, the risk of abortion is relatively low, whereas congenital transmission of *T. gondii* is relatively frequent [33] and this may be explained on the basis of hormone levels and cytokine profiles. Thus, in the first trimester, levels of pregnancy hormones, such as progesterone, are relatively low so there is no or little Th2 cytokine polarization and little chance that the mother will mount a Th1 response to deal with the parasite while in the third trimester, hormone levels are high, the Th2 bias is firmly established; hence, control of the parasite is compromised and congenital transmission occurs. This is supported by evidence from murine studies. For example, pregnant mice are more susceptible to infection with *T. gondii* and this is associated with a reduced ability to produce IFN-γ [34]. Furthermore, administration of Th1 cytokines, such as IFN-γ and IL-2, reduces mortality in pregnant mice infected with *T. gondii* [35]. The immune response of mice to *T. gondii* during pregnancy has also been studied using transgenic IL-4-deficient mice; pregnant wild-type mice are more susceptible than IL-4-deficient mice to toxoplasmosis, showing increased parasite loads. Pregnant IL-4-deficient mice also demonstrate a decreased transmission rate to the foetus when compared with wild-type mice [36].

Neospora Caninum: Neospora is an intracellular protozoan parasites,which stimulate Th1 cytokine responses dominated by cytokines such as IL-12, interferon (IFN) γ and tumour necrosis factor alpha (TNF- α), leading to activation of pathways that generate free oxygen radicals (FOR) and nitric oxide (NO) and its metabolites, among other factors which are potentially lethal for the protozoa [37]. Th1 responses in mice are classically associated with antibodies of the IgG2a isotype plus, potentially, IgG2b and IgG3 isotypes and inhibition of IgG1, IgE and IgM [38]. It is likely that this response is involved in controlling the multiplication of tachyzoites [39]. There is evidence that naturally, chronically infected cattle, have a protective immune response against abortion, but which is ineffective against reactivation of latent infection and infection of the foetus [40]. We know that the timing of foetal infection appears to be critical in determining whether the foetus survives the infectious insult [41,42]. It could be argued that, in a chronically infected cow, the maternal immune system could be primed early in gestation. This would reduce the risk of activation of a latent infection and protect the foetus. Activation of infection later in gestation, once the foetal immune system has started to develop, would pose a lower risk to the foetus. In a naïve animal, only if the infectious onslaught was massive, such as following an intravenous challenge, would the primed immune system be insufficient to protect the foetus. However, in an immune animal, the anamnestic response may be sufficient to control the parasitaemia and hence, protect the foetus.

In humans, studies of the systemic immune response suggested that it is polarized towards a Th2 response during pregnancy. Although studies in pregnant cattle infected with N. caninum did not demonstrate a polarised Th2 response in peripheral blood mononuclear cells [40], it is nevertheless likely that a regulatory response exists in the placenta involving cytokines such as trophoblast growing factor-β (TGF)-β and IL-10 [43]. To compensate for the Th2 bias in pregnant mammals, it is thought that components of the innate immune system are activated in the peripheral blood. Blood monocytes and possibly leukocytes are primed to respond to infectious insult. They express activated phenotypes, increased phagocytic capability, increased respiratory burst activity and are primed to secrete IL-12 [44]. Such a primed innate response in the blood may be highly efficient in eliciting the anamnestic response thus protecting the foetus from an overwhelming exogenous challenge, despite the regulatory Th2 environment in the placenta.

Trypanosomes: African and American trypanosomiasis, among others, are diseases that have an enormous impact on global health and economy. The social consequences of tropical diseases impede development in various ways,

lowering fertility rates, population growth, savings and investment and productivity and raising absenteeism, premature mortality and medical costs [45].

Trypanosomiasis is associated with changes in the activity of several endocrine glands and it seems possible that the infertility observed in trypanosomiasis could be associated with changes in hypothalamo-pituitary adrenal axis (HPA). Rapid increase in ACTH takes place in chronic phase more than acute phase of infection while plasma testosterone showed delayed response and its concentration increased when plasma ACTH and cortisol concentration declined sharply. Testicular degeneration is evident upon palpation of scrotal contents with high deterioration of semen picture. Concentrations of plasma oestradiol 17β and testosterone were significantly different ($P < 0.05$) in camel bulls infected with *T. evansi* when compared to normal ones [47].

T. evansi are involved in the continuous production of more than 1000 genetically controlled antigens (variable surface glycoproteins, VSGs) [48] resulting in the formation of immune complexes to evade the animal immune system as long as the parasite is not eliminated from such an animal [49]. Such immune complexes precipitate under the basement membrane of the seminiferous tubules in the chronically infected bulls [50] causing impairment of the biological functions of junctional complexes, altered metabolism or hyperactivation of the Sertoli cells that may lead to four-fold increase in plasma oestradiol-17β concentrations. It appears from previous observations in the camel [47] and other species [51-53] that a higher concentration of oestrogen suppresses secretion of gonadotropin-releasing hormone (GnRH) and exerts a negative feed-back mechanism on leutinizing hormone (LH) leading to depression in Leydig cell function and maintaining low levels of plasma testosterone (less than 1 ng/ml). The trypanosoma-induced immune complexes and hormonal defects which could impair the sequential divisions and differentiation of germ cells to produce spermatozoa [54] and eventually their adverse effects on sperm concentrations and sperm morphology was observed. Trypanosoma infections reduce T cell responsiveness. T cell proliferation was profoundly suppressed upon mitogenic stimulation and mediated by macrophage-like suppressor cells, leading to suppressed interleukin-2 secretion and impaired expression of the interleukin-2 receptor. A possible explanation for the reduced antibody responses in *T. evansi* infected pigs might reside in a T cell suppression induced by the infection. Indeed, the induction of a good antibody response needs a good T helper cell response as the latter provides help to the B cell through delivery of cytokines. Consequently *T. evansi* infection might interfere with the development of protective immunity upon heterologous vaccinations [55]. Also, for better understanding to the invasion of trypanosomes (*Trypanosoma brucei gambiense or T.b. rhodesiense)* to central nervous cystem and the Mechanisms of blood-brain barrier and blood-cerebrospinal fluid barrier leakage, when *T.b. gambiense* was cultivated on human bone marrow endothelial cell (HBMEC) line to study cell activation, the expression of the adhesion molecules ICAM-1, E-selectin and CAM-1 increased in co-culture. The parasites induced the synthesis of the pro-inflammatory cytokines TNF-α, IL-6 and IL-8 and of nitric oxide (NO) by HBMEC. these molecular soluble factor are responsible for endothelial cell activation and consequently potentiation of the inflammatory reaction, leukocyte recruitment, passage of trypanosomes into the CNS and barrier dysfunction observed during CNS involvement of human African trypanosmoiasis [56].

Also, *T. congolense* clearly affected establishment of pregnancy in infected ewes, as shown by lower rates of pregnancy and extended intervals between breeding and confirmation of pregnancy [57].

Trichomonades: *Trichomonas foetus* (Genital trichomoniasis), most often associated with venereal disease in cattle. Once the organisms are present in the herd, they can be passed from cow to cow by the herd bull (s) or by contaminated breeding equipment. Young bulls usually 'clear' the organisms quite rapidly, but become reinfected upon breeding a cow that is carrying an infection. Older bulls (4-5+ yrs) are more often chronically infected. Cows are able to develop immunity to these organisms, although they can still be infected for up to 3 weeks before the infection is cleared. A 'dirty' white vaginal discharge can occur 1-2 weeks after becoming infected. *T. Vaginalis* is determental of pregnancy in early stages [58].

In human, *T. vaginalis* has been detected in 66-77% of the male partners of infected women and of those men, about 70% were asymptomatic [59]. In men the infection, although usually self-limiting and often asymptomatic, is associated with urethritis, prostatitis, epididymitis, reduced sperm function and infertility [60, 61]. It is important to note that the *T. vaginalis* infection is often recurrent, with no lasting immunity, suggesting the importance of innate immunity. The immunoinflammatory response to trichomoniasis has been most studied in

pregnant women. *T. vaginalis* positive pregnant women had increased vaginal IL-1β and neutrophils [62]. Increased cervical IL-8 and alpha-defensin have been found in pregnant infected women [63] . At the same time, in symptomatic women, anti-inflammatory mediators such as the soluble leukocyte protease inhibitor (SLPI) were lower and reactive nitrogen intermediates, macrophages and CD4+ (helper) T cells were higher. This inflammatory response also leads to the production of TNF-α which activates CD4+ T cells. [64,65]. The presence of increased C-reactive protein in the sera of *T. vaginalis* infected pregnant women suggests that the impact of the immunoinflammatory reaction to the parasite exceeds the boundaries of the reproductive tract mucosa [64].

The immunoinflammatory responses to *T. vaginalis* infection have been studied in vitro and in mouse models. In vitro experimentation has been conducted with cervical and vaginal epithelial cells [66-68] and with various immune cell types [69,70]. Both proinflammatory and immunosuppressive responses have been observed as discussed below. Mice challenged with asymptomatic compared with symptomatic *T. vaginalis* isolates responded by increased IgA, IgG, Th1 cytokines and production of reactive nitrogen intermediates. Both circulating and mucosal antibodies have been detected in women [71]; however, the immunity is not lasting and it has been shown that *T. vaginalis* cysteine proteases present in the serum and vaginal secretions of symptomatic women can degrade IgG, IgM and IgA [72]. In addition, the *T. vaginalis* cysteine proteases including CP30, induce apoptosis in vaginal epithelial cells [73] and in multiple mucosal immune cell types. In leukocyte culture, *T. vaginalis* stimulated IL-8, leukotrienes, reactive nitrogen intermediates and inducible nitric oxide synthase (iNOS) [69, 74]. *T. vaginalis* has been shown to produce leukotrienes capable of activating the host cells [70]. *T. vaginalis* proteins (adhesins and CP30) induce caspase mediated apoptosis cells, macrophages and dendritic cells and production of immunosuppressive cytokines (IL-10, TGF-β) [75,76]. *T. vaginalis*-induced apoptosis in neutrophils has been linked to caspase-3 activation and reduced expression of the anti-apoptotic protein myeloid cell leukemia sequence 1 (Mcl-1) [77] and in macrophages it has been linked to extracellular signal-regulated kinases (ERK) activation [78].

Cytokine Bias after Helminth Infection: Helminthic parasites are diverse in form and life style and are often quite host-specific. Having co-evolved over long periods of time (at least hundreds of millions of years), most parasitic helminths are usually well adapted to making best use of the host and in particular, to living with its immune system. Most of these parasites have developed multiple mechanisms for evading the immune response, either by becoming less recognizable (immunological ignorance) or by direct immunosuppression. Immune responses to tissue-invasive helminths often feature high levels of IgE (mostly not parasite-specific), eosinophilia and mastocytosis, all of which are driven by Type 2 cytokines. However, it should be noted that helminthic parasites often induce very complex responses and also that not all of these special features are necessarily displayed with equal prominence regardless of the parasite species involved. As with immunity to protozoa, what works well for one helminthic parasite species, may not provide protection against another.

Resistance to several species of intestinal nematodes is dependent on Type 2 immune responses. In particular, expulsion of adult nematodes from the gut is dependent on IL-13 and IL-4 [79].

The Type 2 cytokines including IL-3, IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13 do play key roles in specialized immune elements (e.g. mastocytosis, eosinophilia and IgE production).

Toxocara Infection: Toxocara infection is enhanced during pregnancy whereas the larvae grow in liver and lung 1-8 days before parturition and migrate to the mammary gland around the time of parturition [80], then pass into the milk during the first 26 days after parturition [81]. It is common to find buffalo calves highly infected between 15 and 90 days of age with the peak egg output occurring 31-45 days post-infection [80]. Pregnant bitches showed cytokine changes where IL-10 concentrations increased in infected animals and in the meantime IFNγ production increase during 1-2 weeks of gestation and then at 3-8 weeks of gestation IFNγ secreted by infected dogs was slightly higher than normal. These observations could offer us a possible explanation of reactivation of infection during pregnancy. Also IL-10 is increasing with weeks of pregnancy and in the meantime IFNγ is decreasing, it could be possible that during this phase of life through this kind of immunosuppression, mediated by increase of IL-10 and decrease of IFNγ, parasite transmission and/or infection could be favored. In fact IL-10 could inhibit granulomatous response to the parasite through inhibition of IFNγ mediated macrophage activation.

IL-10 and IFNγ were tested also in healthy and infected puppies during the first 10 weeks of life (from 4 to 10 weeks after birth) as in these ages T. canis larval infection is reactivated. IL-10 concentration decreases from 4 to 10 weeks in uninfected or infected puppies while IFNγ assays showed the only statistically significant difference at 10 weeks after birth. During the first phase of puppyhood, Th0/Th2 pattern of cytokines production provides appropriate conditions for progression of the transplacentally acquired infection. In the second and third phases of infancy tested, increasing parasitic antigens lead to induction of immune response polarization while at the same time there is an amplification of TCRs and BCRs repertoires through expansion of the antigen-specific clones caused by their interactions with antigens or ‘‘superantigens [82].

Type 1 and Type 2 cytokine responses may be antagonistic in immunity to helminths, but for tissue dwelling parasites such as Schistosoma mansoni, elements of both are likely to be important in host resistance and in limiting immunopathology. The immune response in.

Schistosomiasis: schistosomiasis is obviously a delicate balancing act, complicated by the likelihood that the parasite utilizes elements of the host defence to enhance its own development and fecundity. Type 1 cytokines predominate in the early stages of infection with *S.mansoni* and may be protective against the stage of the parasite which first penetrates the host via the skin. It is reported that as egg production begins, a shift to Type 2 dominance occurs. Analysis of cross-sectional antibody data (IgA, IgE, IgG1, IgG2, IgG3, IgG4 and IgM directed against Schistosoma haematobium soluble egg antigen (SEA)) showed that cluster analysis partitioned the data into distinct epidemiological groups based on all seven antibody isotypes (defined by age, infection intensity, treatment status and history of infection) confirming an already known partitioning based on IgA/IgG1 production. Also there was a differential distribution of IgE and IgG4 between clusters consistent with the recently proposed balance between Th1, Th2 and regulatory T cells [83]. The cytokine regulation of these antibodies helps to understand the patterns observed; IgE and IgG4 production is induced by IL-4 and IL-13 and inhibited by IFN-γ [84]. IL-4 dependent production of IgE is inhibited by lower levels of IFN-γ than IgG4 production. IgA production is regulated by IL-10 and TGF-β. IL-10 induces mature B-lymphocytes to produce IgG1. TGF-β affects prestimulated B-cells and pre-switched B-cells differentially, so that it inhibits IL-10 mediated secretion of both IgA and IgG1by pre-switched B-cells, but stimulates B-cells to produce IgA. This suggests that the dichotomy observed in IgA and IgG1 responses in this population is due to TGF- β’s different effects on the two antibodies.

Fasciolosis: Fasciolosis is one of the most important parasitic diseases of domestic ruminants. Non-fatal infections, apart from resulting in poor productivity, it affects on the animal fertility causing abortion (during all stages of gestation),and embryonic and neonatal deaths and calf crop of less than 50% of uninfected animals [85].

The effect of single or repetitive fluke-infections on rat liver steroid hormone metabolism was studied by oral administration of 20 metacercariae of *Fasciola hepatica* in rats. The liver of mono-infected rats showed lowered values of hepatic cytochrome P 450 by 36-64% and the expression of isoenzymes necessary for 16a and 2a-hydroxylations of progesterone and testosterone were significantly decreased by 50-90 %, Interestingly, in repetitive fluke infected rats, steroid hormones were metabolized similarly to control normal levels and this could be related to the changes in the animal immune response [86]. However, comparing the effect of liver fluke and gastrointestinal nematodes infections on weight gain and reproductive performance of beef heifers, results revealed that nematodes infection affected body weight gain and reproductive performance significantly more than the liver fluke did [87]. Cattle suffering from fascioliosis showed reduced lymphocyte responsiveness and IFN-γ production after 3-4 weeks of infection and also demonstrate a highly skewed antibody response where IgG1 dominates [88]. Parasite persistence within the host suggests the presence of immune regulatory networks where it initiateTh2 effector mechanisms such as IL-4 and IL-5 secretion. Th1 effector cytokines were suppressed when PBMC’s from infected animal were re-stimulated in vitro with IFNγ production being compromised. Antibody responses were skewed towards IgG1, while IgG2a production was diminished. The magnitude of these effects were seen to be dependent on the final parasite burden [89]. An understanding of how helminths are able to generate immune environments which favour pathogen persistence and chronic infection is important for developing successful strategies for immunoprophylaxis. Modulation of macrophage and dendritic cell function and interaction with toll-like receptors (TLR) are thought

to be some of the fundamental events involved in establishing this immune regulation. Macrophages metabolize L-arginine in two ways either using inducible nitric oxide synthase (iNOS) or arginase (arg). The differential regulation of these enzymes is known to correspond to either classical or alternative macrophage activation (AAMϕ) respectively. iNOS is used as a marker of classical activation, while arginase is used to identify alternatively activated macrophages (AAMF). [90]. It has been reported that F. hepatica infection induces AAMϕ in the murine model. Furthermore, a recombinant version of F. hepatica enzyme peroxiredoxin (Prx) can also induce AAMϕ. Inoculation of mice with Prx created a population of macrophages with suppressed iNOS mRNA levels and elevated TGF-β levels an immune regulatory cytokine [91]. The importance of the effects of this molecule, Prx, is thought to be in the defence of F. hepatica by detoxification of hydrogen peroxide (H2O2) released by the host [92]. The level of H2O2 released by macrophages in the presence of pathogens may also be determined by the phenotype of macrophages. If F. hepatica has evolved an enzyme to detoxify host H2O2 and modulate the macrophage phenotype then it would appear that the parasite defence mechanisms are tightly linked with those of the host.

CONCLUSION

Parasitic infection has significant effect on human and animal health and is responsible for major economic losses in agriculture throughout temperate regions of the globe. Control measures are heavily reliant on chemotherapy resulting in the emergence of drug resistant parasite populations. Novel control strategies ultimately require a deeper knowledge of host-parasite interactions, understanding of the immune response to the infection. Research should make target identification and characterisation more rapid. In parallel, integration of technology with better control measures will help to improve the animal productive performance.

REFERENCES

1. Maldonado, J. and S. Shreif, 2010. Livestock and Product Annual Global Agricultural International Network USDA Foreign Agricultural Service.
2. Colley, D., P. Loverde and L. Savioli, 2001. Medical Helminthology in the 21st Century, Science, 293: 1437-1438.
3. Waller, P., 2003, Global perspectives on nematode parasite control in ruminant livestock: The need to adopt alternatives to chemotherapy, with emphasis on biological control, Anim. Health. Res. Reviews, 4: 35-43.
4. Sekoni, V.O., 1994. Reproductive disorders caused by animal trypanosomosis: A review. Theriogenology, 42: 557-570.
5. Ahmed, W.M., H.H. El-khadrawy, F.M. El Moghazy, E.M. Hanafi, M.M. Romany and S.M. Habeeb, 2010. Field Observations On The Relationship Between Babesiosis and Reproductive Disorders In Female buffaloes International Journal Of Academic Research, 2: 341-348.
6. Okech, G., E.D. Watson, A.G. Luckins and D.W. Makawiti., 1996. The effect of trypanosoma vivax infection on late pregnancy and postpartum return to cyclicity in Boran cattle. Theriogenology, 46: 859-869.
7. Grabitzki, J. and G. Lochnit, 2009 Immunomodulation by phosphocholine Biosynthesis, structures and immunological implications of parasitic PC-epitopes Molecular Immunology, 47: 149-163.
8. Mosmann, T.R. and R.L. Coffman, 1989. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. Annu. Rev. Immunol., 7: 145-173.
9. Dent, L.A., G.H. Munro, K.P. Piper, C.J. Sanderson, D.A. Finlay, R.K. Dempster, L.P. Bignold and D.G. Harkin, Hagan, 1997. Eosinophilic interleukin 5 (IL-5) transgenic mice: eosinophil activity and impaired clearance of Schistosoma mansoni. Parasite Immunol., 19: 291-300.
10. Medawar, P.B., 1953. Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates. Symp. Soc. Exp. Biol., 7: 320-338.
11. Raghupathy, R., 1997. Th1-type immunity is incompatible with successful pregnancy. Immunol. Today., 18: 478-482.
12. Sacks, G.P., C.W. Redman and I.L. Sargent, 2003. Monocytes are primed to produce the Th1 type cytokine IL-12 in normal human pregnancy: an intracellular flow cytometric analysis of peripheral blood mononuclear cells. Clin. Exp. Immunol., 131: 490-497

13. Pollard, J.W., J.S., Hunt, W. Wiktor-Jedrzejczak and E.R. Stanley, 1991. Pregnancy defect in the osteopetrotic (op/op) mouse demonstrates the requirement for CSF-1 in female fertility. Biology, 148: 272-283.
14. Irving, J.A. and P.K. Lala, 1995. Functional role of cell surface integrins on human trophoblast cell migration: regulation by TGF-IGF-II and IGFBP-1. Experimental Cell Research, 217: 419-427.
15. Brach, M.A., S. de Vos, H.J. Gruss and F. Herrmann, 1992. Prolongation of survival of human polymorphonuclear neutrophils by granulocyte-macrophage colony-stimulating factor is caused by inhibition of programmed cell death. Blood, 80: 2920-2924.
16. Arck, P.C., J. Dietl and D.A. Clark, 1999. the decidual cell internet: trophoblast-recognising T cells. Biology of Reproduction, 60: 227-233
17. Bazer, F.W., T.E. Spencer and T.L. Ott, 1997. Interferon tau: a novel pregnancy recognition signal. American Journal of Reproductive Immunology, 37: 412-420.
18. Tangri, S. and R. Ragupathy, 1993. Expression of cytokines in placentae of mice undergoing immuno-logically mediated spontaneous fetal resorptions. Biology of Reproduction, 49: 850-856.
19. Chaouat, G., 2003. Innately moving away from the Th1/Th2 paradigm in pregnancy. Clin. Exp. Immunol, 131: 393-395
20. Aluvihare, V.R., M. Kallikourdis and A.G. Betz, 2004. Regulatory T cells mediate maternal tolerance to the fetus. Nat. Immunol, 5: 266-271
21. Devereux, G., 2006. The increase in the prevalence of asthma and allergy: food for thought. Nat. Rev. Immunol, 6: 869-874.
22. Arck, P., P.J. Hansen, J.B. Mulac, M.P. Piccinni and J. Szekeres-Bartho, 2007. Progesterone during pregnancy: endocrine-immune cross talk in mammalian species and the role of stress. Am. J. Reprod. Immunol., 58: 268-279.
23. Entrican, G. and N. Wheelhouse, 2006. Immunity in the female sheep reproductive tract. Vet. Res., 37: 295-309.
24. Kalinski, P., C.M. Hilkens, A. Snijders, F.G. Snijdewint and M.L. Kapsenberg, 1997, IL-12-deficient dendritic cells, generated in the presence of prosta-glandin E2, promote type 2 cytokine production in maturing human na¨ýve T helper cells. Journal of Immunology, 159: 28-35.
25. De-Mouzon, H. and M. Millo, 2006 The placenta cytokine network and inflammatory signals. Placenta, 27: 794-798.
26. Hansen, P. and W. Liu, 1996. Immunological aspects of pregnancy: concepts and speculations using the sheep as a model. Anim. Reprod. Sci., 42: 483-493
27. Gunnink, J.W., 1984 Retained placenta and leucocytic activity. Vet Quart, 6: 49-51.
28. Quinn, H.E., J.T. Ellis and N.C. Smith, 2002. Neospora caninum: another protozoan parasite that causes immune-mediated failure of pregnancy? Trends Parasitol., 18: 391-394.
29. Krishnan, L., L.J. Guilbert, A.S. Russell, T.G. Wegmann, T.R. Mosmann and M. Belosevic, 1996. Pregnancy impairs resistance of C57BL/6 mice to eishmania major infection and causes decreased antigenspecific IFN-gamma responses and increased production of T helper 2 cytokines. J. Immunol., 156: 644-652.
30. Krishnan, L., L.J. Guilbert, T.G. Wegmann, M. Belosevic and T.R. Mosmann, 1996. T Helper 1 response against Leishmania major in pregnant C57BL/6 mice increases implantation failure and fetal resorptions J. Immunol., 156: 653-662.
31. Owen, M.R. and A.J. Trees, 1998. Vertical transmission of Toxoplasma gondii from chronically infected house (Mus musculus) and field (Apodemus sylvaticus) mice determined by polymerase chain reaction. Parasitology, 116: 299-304.
32. Moormann, A.M., A.D. Sullivan, R.A. Rochford, S.W. Chensue, P.J. Bock, T. Nyirenda and S.R. Meshnick, 1999. Malaria and pregnancy: placental cytokine expression and its relationship to intrauterine growth retardation. J. Infect. Dis., 180: 1987-1987.
33. Roberts, C.W., 2001. Sex-associated hormones and immunity to protozoan parasites. Clin. Microbiol. Rev., 14: 476-488.
34. Shirahata, T., 1992. Correlation between increased susceptibility to primary Toxoplasma gondii infection and depressed production of gamma interferon in pregnant mice. Microbiol. Immunol., 36: 81-91.
35. Shirahata, T., 1993. Enhancement by recombinant human interleukin 2 of host resistance to Toxoplasma gondii infection in pregnant mice. Microbiol. Immunol., 37: 583-590.

36. Houvenin, M., 1997. Immune response in a murine model of toxoplasmosis: increasedsusceptibility of pregnant mice and transplacental passage of T. gondii are type-2 dependent. Parassitologia, 39: 279-283
37. Hunter, C.A. and S.L. Reiner, 2000. Cytokinesand T cells in host defence. Curr. Opin. Immunol., 12: 413-418.
38. Wang, Z.H., 1994. CD4+ effector cellsdefault to the Th2 pathway in interferon γ-deficient mice infected with Leishmania major. J. Exp. Med., 179: 1367-1371
39. Innes, E.A., 1995. Interferon gamma inhibits the intracellular multiplication of Neospora caninum, as shown by incorporation of 3H Uracil. J. Comp. Pathol., 113: 95-100
40. Williams, D.J.L., C.S. Guy, J.W. McGarry, F. Guy, L. Tasker, R.F. Smith, K. MacEachern, P.J. Cripps, D.F. Kelly and A.J. Trees, 2003. Neospora caninum-associated abortion in cattle: the time of experimentally-induced parasitaemia during gestation determines foetal survival. Parasitology. 121: 347-358.
41. Williams, D.J.L., 2000. Neospora caninum associated abortion in cattle: the time of experimentally-induced parasitaemia during gestation determines foetal survival. Parasitology, 121: 347-358
42. Guy, C.S., D.J.L. Williams, D.F. Kelly, J.W. McGarry, F. Guy, C. Bjo¨rkman, R.F. Smith and A.J. Trees, 2001. Neospora caninum in persistently infected pregnant cows: spontaneous transplacental infection is associated with an acute increase in maternal antibody. Vet. Rec., 149: 443-449.
43. Miller, L. and S. Munn, 2000, Progesterone inhibits inducible nitric oxide synthase gene expression and nitric oxide production in murine macrophages. J. Leukoc. Biol., 59:442-450.
44. Sacks, G., I. Sargent and C. Redman, 1999, An innate view of human pregnancy. Immunology Today, 20: 114-118.
45. Reguera, R.M. L.T. Babu and B. Rafael, 2005. Polyamine transport in parasites: A potential target for new antiparasitic drug development Comparative Biochemistry and Physiology, Part C, 140: 151-164.
46. Mutayoba, B.M., P.D. Eckerisall and C. Seely, 1995. Effect of Trypanosoma congolense on pituitary and adrenocortical function in sheep: resposes to exogenous corticotrophin-releasing hormone. Research in Veterinary Science, 58: 180-185.
47. Al-Qarawi, A.A., H.M. Omar, H.A. Abdel-Rahman, S.A. El-Mougy and M.S. El-Belely, 2004. Trypanosomiasis-induced infertility in dromedary (Camelus dromedarius) bulls: changes in plasma steroids concentration and semen characteristics Animal Reproduction Science, 84: 73-82
48. Turner, C.M.R., 2001. Opsonization of trypanosomes. In: Halton, D.W., Behnke, J.M., Marshall, I. (Eds.), Practical Exercises in Parasitology. Cambridge University Press.
49. Hyneman, D., 1998. Medical parasitology. In: Books, G.F., Butel, J.S., Moris, A. (Eds.), Medical Microbiology.Appleton and Lang, Stamford, CT, USA.
50. Tizard, I., 1996. Veterinary Immunology: An Introduction. WB Saunders Company, London, Toronto.
51. Schanbacher, B.D., 1979. Relationship of *in vitro* gonadotrophin binding to bovine testis and the onset of spermatogenesis. J. Anim. Sci., 48: 591-597.
52. Amann, R.P., 1983. Endocrine changes associated with onset of spermatogenesis in Holstein bulls. J. Dairy Sci., 66: 2606-2622.
53. Payne, A.H., 1990. Hormonal regulation of cytochrome P450 enzyme, cholesterol side-chain cleavage and oestradiol 17_-hydroxylase/ C17–20lyase in Leydig cells. Biol. Rep., 42: 399-404.
54. Sharpe, R.M., 1984. Intratesticular factors controlling testicular function. Biol. Rep., 30: 29-35.
55. Holland, W.G., T.T. Dob, N.T. Huongb, N.T. Dungb, N.G. Thanh, J. Vercruysse and B.M. Goddeeris, 2003. The effect of Trypanosoma evansi infection on pig performance and vaccination against classical swine fever Veterinary Parasitology, 111: 115-123.
56. Girard, M., S. Giraud, C. Bertrand, Marie-Odile, Jauberteau-Marchan and Bernard Bouteille, 2005. Endothelial cell activation in the presence of African trypanosomes Molecular and Biochemical Parasitology, 139: 41-49.
57. Osaer , B., I.B. Goossens, J. Jeffcoate, A. Jaitner and S.P. Kora, 1998, Holmes Effects of Trypanosoma congolense and nutritional supplements on establishment and outcome of pregnancy in trypanotolerant Djallonke´ ewes Animal Reproduction Science, 51: 97-109.

58. Fichorova, R.N., R.T. Trifonova, R.O. Gilbert, C.E. Costello, J.J. Hayes and G.R. Lucas, 2006. Trichomonas vaginalis lipophosphoglycan triggers a selective upregulation of cytokines by human female reproductivetract epithelial cells. Infect. Immun., 74: 5773-5779.
59. Sena, A.C., W.C. Miller, M.M. Hobbs, J.R. Schwebke, P.A. Leone and H. Swygard, 2007. Trichomonas vaginalis infection in male sexual partners: implications for diagnosis, treatment and prevention. Clin. Infect. Dis., 44: 13-22.
60. Singh, B.N., J.J. Lucas and R.N. Fichorova, 2007. Trichomonas vaginalis: pathobiology and pathogenesis. In: Khan, N.A., et al. (Eds.), Emerging Protozoan Pathogens. Taylor and Francis Group, London, UK, pp: 411-455.
61. Benchimol, M., I. de Andrade Rosa, R. da Silva Fontes and A.J. Burla Dias, 2008. Trichomonas adhere and phagocytose sperm cells: adhesion seemsto be a prominent stage during interaction. Parasitol. Res., 102: 597-604.
62. Cauci, S. and J.F. Culhane, 2007. Modulation of vaginal immune response among pregnantwomenwith bacterial vaginosis by Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae and yeast. Am. J.Obstet. Gynecol, 196(133): 131–137.
63. Simhan, H.N., B.L. anderson, M.A. Krohn, R.P. Heine, B. Martinez de Tejada and D.V. Landers, 2007. Host immune consequences of asymptomatic Trichomonas vaginalis infection in pregnancy. Am. J. Obstet. Gynecol., 196(59): 51-55.
64. Al-Mohammed, H.I. and E.M. Hussein, 2006. Comparison between secretory leukocytic protease inhibitor and reactive nitrogen intermediates levels in cervicovaginal secretions from symptomatic and asymptomatic trichomoniasis Egyptians patients. J. Egypt Soc. Parasitol., 36: 763-777.
65. Draper, D., W. Donohoe, L. Mortimer and R.P. Heine, 1998. Cysteine proteases of Trichomonas vaginalis degrade secretory leukocyte protease inhibitor. J. Infect. Dis., 178: 815-819.
66. Bastida-Corcuera, F.D., C.Y. Okumura, A. Colocoussi and P.J. Johnson, 2005.Trichomonas vaginalis lipophosphoglycan mutants have reduced adherence and cytotoxicity to human ectocervical cells. Eukaryot. Cell, 4: 1951-1958.
67. Okumura, C.Y., L.G. Baum and P.J. Johnson, 2008. Galectin-1 on cervical epithelial cells is a receptor for the sexually transmitted human parasite Trichomonas vaginalis. Cell Microbiol., 10: 2078-2090
68. Sommer, U., C.E. Costello, G.R. Hayes, D.H. Beach, R.O. Gilbert and J.J. Lucas, 2005. Identification of Trichomonas vaginalis cysteine proteases that induce apoptosis in human vaginal epithelial cells. J. Biol. Chem., 280: 23853-23860.
69. Ryu, J.S., J.H. Kang, S.Y. Jung, M.H. Shin, J.M. Kim and H. Park, 2004. Production of interleukin-8 by human neutrophils stimulated with Trichomonas vaginalis. Infect. Immun., 72: 1326-1332.
70. Shaio, M.F., P.R. Lin, J.Y. Liu and K.D. Yang, 1995. Generation of interleukin-8 from human monocytes in response to Trichomonas vaginalis stimulation. Infect. Immun., 63: 3864-3870.
71. Kaur, S., S. Khurana, R. Bagga, A. Wanchu and N. Malla, 2008. Antitrichomonas IgG, IgM, IgA and IgG subclass responses in human intravaginal trichomoniasis. Parasitol. Res., 103: 305-312.
72. Yadav, M., M.L. Dubey, I. Gupta and N. Malla, 2007. Cysteine proteinase 30 (CP30) and antibody response to CP30 in serum and vaginal washes of symptomatic and asymptomatic Trichomonas vaginalis infectedwomen. Parasite Immunol., 29: 359-365.
73. Sommer, U., C.E. Costello G.R. Hayes, D.H. Beach, R.O. Gilbert and J.J. Lucas, 2005. Identification of Trichomonas vaginalis cysteine proteases that induce apoptosis in human vaginal epithelial cells. J. Biol. Chem., 280: 23853-23860.
74. Shaio, M.F., P.R. Lin, C.S. Lee, S.C. Hou, P. Tang and K.D. Yang, 1992. A novel neutrophil-activating factor released by Trichomonas vaginalis. Infect.Immun., 60: 4475-4482.
75. Chang, J.H., Y.S. Ryang, T. Morio, S.K. Lee and E.J. Chang, 2004. Trichomonas vaginalis inhibits proinflammatory cytokine production in macrophages by suppressing NF-kappaB activation. Mol. Cells, 18: 177-185.
76. Chang, J.H., J.Y. Park and S.K. Kim, 2006. Dependence on p38 MAPK signalling in the up-regulation of TLR2, TLR4 and TLR9 gene expressionin Trichomonas vaginalis-treated HeLa cells. Immunology, 118: 164-170.
77. Kang, J.H., H.O. Song, J.S. Ryu, M.H. Shin, J.M. Kim and Y.S. Cho, 2006. Trichomonas vaginalis promotes apoptosis of human neutrophils by activating caspase-3 and reducing Mcl-1 expression. Parasite Immunol, 28: 439-446.

78. Chang, J.H., S.K. Kim, I.H. Choi, S.K. Lee, T. Morio and E.J. Chang, 2006. Apoptosis of macrophages induced by Trichomonas vaginalis through the phosphorylation of p38 mitogen-activated protein kinase that locates at downstream of mitochondria-dependent caspase activation. Int. J.Biochem. Cell Biol., 38: 638-647.
79. Urban, J.F., N. Noben-Trauth, D.D. Donaldson, K.B. Madden, S.C. Morris, M. Collins and F.D. Finkelman, 1998. IL-13, IL4R and Stat6 are required for the expulsion of the gastrointestinal nematode parasite Nippostrongylus brasiliensis. Immunity, 8: 255-264.
80. Roberts, J.A., 1990. The egg production of Toxocara vitulorum in Asian buffalo (Bubalus bubalis). Int. J. Parasitol, 37: 113-120.
81. Starke, W.A., R.Z. Machado and M.C. Zocoller, 1992. Transmammary passage of gastrointestinal nematode larvae to buffalo calves. II. Toxocara vitulorum larvae. Arq. Bras. Med. Vet. Zoot., 44: 97-103.
82. Torina, A., S. Caracappa, A. Barera, F. Dieli, G. Sireci, C. Genchi, P. Deplazes and A. Salerno. 2005. Toxocara canis infection induces antigen-specific IL-10 and IFNγ production in pregnant dogs and their puppies. Veterinary Immunology and Immunopathology, 108: 247-251.
83. Mutapi, F., P. MEJ Hagan, T. Woolhouse, P. Mduluza and D. Ndhlovu, 2005. Chemotherapy-induced,age- related changes in antischistosome antibodyresponses. Parasit Immunol., 25: 87-97.
84. King, C.L., C.C. Low and T.B. Nutman, 1993. IgE prodcution in human helminth infection reciprocal interelationship between IL-4 and IFN-_. J Immunol, 150: 1873-80.
85. Foreyt, W.J., 1982. The role of liver fluke in infertility of beef cattle. In: Proceedings of the 14th Annual Conference American Association of Bovine Practitioners, Nashville, TN, pp: 99-103.
86. Robin, J.F., G. Mulcahy and H.M. Elsheikha, 2010. Coordinating innate and adaptive immunity in Fasciola hepatica infection: Implications for control Veterinary Parasitology, 169: 235-240.
87. Loyacano, A.F., J.C. Williams, J. Gurie and A.A. DeRos, 2002. Effect of gastrointestinal nematode and liver fluke infections on weight gain and reproductive performance of beef heifers Veterinary Parasitology, 107: 227-234.
88. Clery, D., P. Torgerson and G. Mulcahy, 1996. Immune responses of chronically infected adult cattle to Fasciola hepatica. Vet. Parasitol, 62: 71-82.
89. O'Neill, S.M., M.T. Brady, J.J. Callanan, G. Mulcahy, P. Joyce, K.H. Mills and J.P. Dalton, 2000. Fasciola hepatica infection downregulates Th1 responses in mice. Parasite Immunol., 22: 147-155.
90. Gordon, S., 2002. Alternative activation of macrophages. Nat. Rev. Immunol., 3: 23-35.
91. Donnelly, S.O., S.M. Sekiya, M. Mulcahy and G. Dalton, 2005. Thioredoxin peroxidase secreted by Fasciola hepatica induces the alternative activation of macrophages. Infect. Immun., 73: 166-173.
92. Sekiya, M., G. Mulcahy, J.A. Irwin, C.M. Stack, S.M. Donnelly, X. Weibo, P. Collins and J.P. Dalton, 2006. Biochemical characterization of recombinant peroxiredoxin (FhePrx) of the liver fluke, Fasciola hepatica. FEBS Letter, 580: 5016-5022.