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IMMUNOMODULATION BY CYTOKINES IN CHRONOBIOLOGICAL VISION

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ABSTRACT

Immune system to maintain homeostasis operates through of a network of signaling and components, of which to be detached the cytokines. According with the cytokine profile predominant in place, a type of immune response is induced and can be classified into Th1, Th2, Th3, Th17 and regulatory T cells. The cytokines also are influenced by circadian rhythms. Hormones that suffer chronobiological variations as the cortisol, melatonin, prolactin, growth hormone (GH), and sex hormones may modulate the immune system. Cortisol is an anti-inflammatory and immunosuppressive. The melatonin can lead to increase of proinflammatory cytokines and anti-inflammatory cytokines, exerting a conflicting effect, modulating the immune response so dose-dependent. The GH and prolactin are immunostimulants, as well as promoting the activity of cytokines of the Th1 profile. Estrogens have anti-inflammatory activity, but also can have a proinflammatory role depending on the factors stimulating. Generally the estrogen has stimulatory action in humoral immunity and the progesterone can present a natural immunosuppressive agent and has anti-inflammatory and immunosuppressive properties. Already, the testosterone can reduce the functions of the immune system. This knowledge out is of clinical importance for a possible simultaneous co-stimulation of cells with hormones and cytokines, as typically occurs under physiological conditions in animals and humans. This is a vast field of study and further investigations involving chronoimmunomodulation

need to be more developed. Through this knowledge new applicability involving the immune response and therapies can be proposed.

Keywords: chronoimmunomodulation, cytokines, immunomodulation.

INTRODUCTION

Cytokines and profile response of Helper T Cells

The immune system, through a complex network of interactions, acts with purpose to maintain homeostasis front a pathogenic agent. Immunity can not be fully protective, without causing damage to the host. The balance between the protection and tissue damage is, therefore, essential for the establishment of protection and homeostasis (BARNABA et al., 2012). Stimuli from internal sources, as well as external, should be recognized and processed to make an appropriate decision to response that is "self" and "non-self". This interactive network operates with a high level of complexity, inducing or suppressing other immune system cells (OZDEMIR et al, 2009) that interacts each other to ensure the survival of the host (BARNABA et al., 2012).

The eliminations of invaders pathogens and death prevention, or chronic infection, depend on the the successful collaboration of the innate and adaptive immunity components. The innate immune system is of vital importance in the initial sensing against micro-organisms (HEEGERA & KEMPERB, 2012). The interaction of the innate and adaptive immune response generates an immune response to greater effectiveness in combating a wide variety of micro-organisms found in the host (OLIPHANT et al.,2011). The cells, cytokines and chemokines released during the innate immunity are essential for the initiation and determining of type of response developed during the adaptive response (VERNAL & GARCIA-SANZ, 2008). It is through this signaling network that the immune response is developed, and among these components, is highlighted the cytokines.

Cytokines are inducers proteins that mediate intercellular communication in the immune system (CAMACHO-ARROYO et al., 2009). They can act on the cells that secrete (autocrine action), on the neighboring cells (paracrine action) or, in some cases, in distant cells (endocrine activity) (ZHANG & AN, 2007). They are induced by specific stimuli and are responsible for the generation, differentiation, stimulation of multiple types of cells, as well as by control of production of other cytokines that can enhance or inhibit the synthesis of

products and / or the biological effects of other types of cells and proteins (CURFS, et al, 1997).

A single cytokine can be secreted by different types of cells and a single cytokine may act in different cell types, which is called pleiotropy. Different cytokines can have similar functions, as well as they can act synergistically or antagonists mode (ZHANG & AN, 2007). They are grouped into several protein families, are examples: the tumor necrosis factor (TNF), interleukin (IL) and colony-stimulating factors (CSF) (CAMACHO-ARROYO et al., 2009). Due to the increasing number of cytokines are being discovered is almost impossible to remember all the cytokines and their biological effects (CURFS, et al, 1997).

Cytokines are produced by several cell populations, but the predominant producers are macrophages and T helper lymphocytes (ZHANG & AN, 2007). The role of CD4+ T lymphocytes in host defense and immunoregulation has been well appreciated. This is possible through the differentiation of CD4+ T helper subsets specialized in response to different pathogens, which evoke a distinct environment of cytokines (HIRAHARA, 2011).

The T helper (Th) lymphocytes were defined by cytokines profile produced and were divided into Th1, Th2, Th17 and regulatory T cells (WAISMAN, 2011), Th3 cells are also reported and have regulatory function (WEINER, 2001).

Initially the CD4+ T helper lymphocytes were classified in subtypes, Th1 and Th2, with different functions in the immune response in according to the profile of cytokines produced (MOSMANN et al., 1986). Th1 cells are characterized by secretion of IL-1, INF-γ and TNF-α , (OZDEMIR et al, 2009), in addition to IL-2 and IL-12, and are involved in the eradication of intracellular pathogens (VERNAL & GARCIA-SANZ, 2008), response against tumors, virus, intracellular bacteria, also generate a response involving CD4+ T cells of type Th1 (HEO et al., 2010). Already the CD4+ T cells of Th2 type produce cytokines such as IL-4, IL-5, IL-9 and IL-13 (OLIPHANT et al., 2011) the production of IL-6 is also reported (VERNAL & GARCIA-SANZ, 2008), the Th2 type cells are associated with helminth parasitic infections and inflammatory conditions such as asthma and allergies (OLIPHANT et al., 2011)

Subsequently the classification given by Mosmann and colleagues (1986) of subtypes Th1 and Th2, were described other subtypes of CD4+ T cells, both subtypes with effectors such as

regulators effects, among them, the cells Th17 and regulatory T cells, including Tr1 and Tr Foxp3+ (POT et al. 2011).

The Th17 cell subtype is characterized by the production of the cytokine IL-17, this has proinflammatory property and is involved in inflammatory processes and autoimmune diseases. The cytokines IL -17 family, as the IL-17A and IL-17F, promote antibacterial and anti-fungal responses, the IL-17E is essential in the defense against parasitic infections. The IL-17C, specifically regulates the epithelial immunity, promoting the antibacterial response in barrier surfaces. (PAPPU et al., 2012).

The actions of the Th17 cells profile are mediated by TGF-β1 and IL-6 together with IL-23 (HEO et al., 2010). The cells Th17 also produce other cytokines such as IL-9, IL-10, IL-21, IL-22 and IL-26 (HIRAHARA et al., 2011). These cells are important for the defense of the host in immune responses against extracellular micro-organisms, chronic inflammatory diseases and autoimmune diseases (HUBER, 2011). Because of proinflammatory activity of CD4+ T cells of type Th17 and the possible damages caused by them, their response needs to be well regulated (HUBER, 2011). The IL-10 is one of the keys immunomodulators for regulating of the immune system (SHIN, 1998).

IL-10 is a multifunctional cytokine with diverse effects on hematopoietic cell types. Its main function seems to be the limit and finalise the inflammatory responses (MOORE, 2001). IL-10 also has the ability to downregulation in cytokine expression of TH17 cells profile and can increase regulatory T-cells (HEO et al., 2010).

The CD4+ T regulatory lymphocytes are responsible for maintaining immune homeostasis and various effectors functions, studies have been conducted to understand the molecular and cellular mechanisms involved in Tregs (OZDEMIR et al., 2009). The regulatory T cells (Treg) of type Tr1 are groups of regulatory T cells characterized by production of IL-10. Although initial studies pointed to a paper mediator central of IL-10 in the generation of Tr1, recent studies indicate that the generation Tr1 can also be dependent on IL-27 (KUSHWAH & HU, 2011). About the Foxp3+ regulatory T cells, they are identified by expression of CD25 (IL-2 receptor) and by transcription factor Foxp3, essential for the differentiation of Tregs. They are essential for the maintenance of immune tolerance, prevention of autoimmune reactions and pathology inflicted by uncontrolled immune responses against an infection (ZHENG & RUDENSKY, 2007).

Among the CD4+ T lymphocytes with regulatory function are the helper T cells of the profile Th3, these cells secrete TGF- β and may be independent of IL-2 for its induction and differentiation which distinguishes of Treg thymus-derived cells (CARRIER et al, 2007). The Th3 cells were discovered in mice as mediators of oral tolerance acting to inhibit the induction of the immunity through secretion of transforming growth factor-beta (TGF-β) (WEINER, 2001). Therefore, they play an important role in induction and maintenance of peripheral tolerance, release TGF-β that contribute to induction of regulatory T cells (Foxp3+), which may serve to maintain or restore peripheral tolerance (CARRIER et al, 2007).

The subpopulations of CD4+ T cells develop different responses through of a restricted interaction and balance between them (LOCHNER et al., 2008; OZDEMIR et al, 2009) the knowledge of this interaction is basic to understand one of the mechanisms of development of immune response. That allows the understanding of how the body maintains the homeostatic balance between aggression and suppression. For this, it is believed that the inhibitory activity of the immune system is predominant (ZHANG & AN, 2007). This way the balance is maintained and damage to the host is avoided.

In the case of Th1 cells, for example, they secrete mediators of inflammation, proinflammatory cytokines such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α), while cells Th2 secrete cytokines anti-inflammatory, such as IL-4, IL-10, and IL-13 (MOSMANN, 1996). There is a mutual interaction between the Th1cytokine profile, IFN-γ, Th2 cytokine profile, IL-4. IL-4 is the dominant factor for the promotion of growth and differentiation of T cells for the subtype Th2 and directly inhibits the development of Th1 cells (O'GARRA & ARAI, 2000). Is the IL-4, although its initial source is not completely known, the cytokine key which activates the T cells of Th2 type (KOYASU & MORO, 2011). Already the development of Th1 cells profile is dependent on IFN- γ and the maintenance of this phenotype depends on the stimulus in the presence of IL-12 and IL-18 (O'GARRA & ARAI, 2000).

Similar relationship also occurs in the homeostasis of Treg and Th17 cells that can be balanced by the cytokines environment. The TGF-β is involved in both pathways, and the IL-6 is a cytokine decisive. In the absence of IL-6, TGF-β induces the creation of Treg cells which in turn produce TGF-β and control the inflammation and autoimmunity by suppression of T helper cells. In the presence of IL-6 there is a formation of more cells of type Th17

(GONZALEZ-GARCIA et al. 2009). In the absence of IL-23, the cells Th17 can also produce IL-10. In a study of Heo and colleagues (2010) with patients with rheumatoid arthritis, it was found that the IL-17 and over-expressed in these patients, and this cytokine can increase the production of regulatory T cells and decrease the release of IL-17 and consequently minimize proinflammatory activity.

It is essential to the understanding of immunomodulation by cytokines and the type of response to be activated, because there are special cases that a change in the cytokine environment, leads to an imbalance between the profiles of T helper cells. These changes can be severe, as can occur in pregnancy. According to Sykes and colleagues (2012) during pregnancy, an excessive alteration in the Th cells profiles can lead to damage in pregnancy. Pregnancy is an immune state complex in which a deviation in the direction of T helper 2 protects the fetus. Evidence suggests that the proinflammatory cytokines increase the risks of miscarriages in pregnancy. These proinflammatory cytokines are also released in diseases immune-inflammatory, such as rheumatoid arthritis and asthma. But other concepts involve the understanding of these diseases, such as fluctuations in the release of cytokines that occurs in function of time (PETROVSKY et al., 1998). This knowledge also proportionates us a means of creating new therapies, new means of intervention and prevention. But for this to be achieved it is necessary to have a lot more ample view than just the immunomodulating by cytokines, understand their interactions with some endogenous hormones and the temporal fluctuations that affect them is fundamental to the development of research on the subject that can bring new perspectives about immunomodulation of cytokines in chronobiological vision.

Hormones X cytokines: a chronobiological vision

Life is organized in cycles, physiological and behavioral system is subjected to daily variations, and these daily rhythms are generated by an internal biological clock that is synchronized in 24 hours, following the environment, especially the light / dark cycle (LAPOSKY, et al. 2008). The circadian pacemaker resides in the brain, in the suprachiasmatic nucleus of the hypothalamus (SADKI et al, 2007). This biological clock influence the maintenance of activities such as sleep, temperature regulation, the rates of metabolism, immune responses, blood pressure and hormonal secretion (SADEK et al, 2011). It is through a network of interactions between the neuro-immuno-endocrine system one of

the ways by which the circadian rhythms of living organisms are constituted integrally to maintain homeostasis.

The immune cells also undergo variations according to the fluctuations of the circadian rhythm. It is believed that changes in subsets of the population of lymphocyte also depend on the variations of 24h, the proliferative capacity in immunocompetent organs, as well as the time of day and can change the liberation the traffic of lymphocytes among lymphoid organs (CHACON et al, 2002). Also it checked robust variations of cytokines and cytolytic factors of NK cells, in animals, suggesting strongly that these functions also are subject to regulation circadiana (LOGAN et al, 2011). Evidence suggests that the immune condition, cytokines and other immune mediators may also influence in the temporalization of circadian processes (COOGAN & WYSE, 2008). According Sadki and colleagues (2007) the central nervous system responds differently to cytokines during the night and day, which may also indicate that cytokines may play a role in the function of the biological clock.

The daily rhythms are also influenced by cyclical production of hormones, such as, for example, cortisol and melatonin therefore believe that several of the major components of the inflammatory response, including cytokines and hormones, can suffer significant diurnal variation in its plasma concentrations (SCHEFF et al., 2010).

The cortisol, an endogenous glucocorticoid, is a powerful anti-inflammatory agent and immunosuppressant that is many times used in the treatment of numerous autoimmune and inflammatory diseases (XIANG & MARSHALL, 2011). In healthy subjects, the circadian rhythm of cortisol is characterized by a maximal secretion in the morning, a progressive decline of production over the day to reach the nadir in the evening, immediately after falling asleep, and a subsequent gradual increase over the night up to the morning peak (MONTELEONE et al., 2011. The maximum peak occurs around 8:00 in the morning and the lowest point is found at midnight, an up-regulation is observed in the early morning is probably related to the inhibition of inflammation during the day, and its down-regulation during the night, and it is this period which is related to an increase in inflammation during the overnight. (CUTOLO& STRAUB, 2008).

The cortisol, in serum levels higher, presents a negative correlation between the levels of lymphocytes during the photoperiod (06:00, 10:00 and 14:00 hours), but in elderly patients have evidenced a positive correlation between cortisol and T-helper/ inducer T lymphocytes

at 14:00 hours, maybe in relationship to the altered circadian rhythmicity of this subpopulation (MAZZOCCOLI et al., 2011).

Glucocorticoids may also modulate the expression of gene involved in the development of innate immune response, while their actions on the adaptive immune response, including the regulation of magnitude and the balance between the responses mediated by CD4 + T cells, as Th1 and Th2 (XIANG & MARSHALL, 2011). The cortisol may not be the only neuroendocrine hormone that entrains the rhythms of cytokines, other candidates include hormones such as: the 17-hydroxy -progesterone and melatonin (PETROVSKY & HARRISON, 1998).

The melatonin has access to a great part of the cells and may exert effects on the immune system. It is believed that the likely effects of melatonin on immune cells may be related to the influence of this hormone in the release of other cytokines and / or other hormones, or by acting directly on the process of phagocytosis (LIEBMANN et al., 1997; RODRIGUEZ et al., 1999). In a study done by França and collaborators (2009), on the study of the effect of melatonin on the chronoimmunomodulation of blood phagocytes, the results showed an increase in the bactericidal activity of phagocytes when stimulated with melatonin and found that this process is influenced by time.

Melatonin plays a role in immunomodulation it stimulates helper T lymphocytes to release cytokines such as IL-2 and IL-4 (MAZZOCCOLI, 2011). Cytokines of Th1 profile as: IFN-γ, IL-1, IL-2, IL-6, IL-12 and TNF-α reach their peak during the night and early morning, at the same time that the serum melatonin is the highest and plasma cortisol is lowest (CUTOLO et al., 2005). In a study conducted by Sutherland (2002) the melatonin was proinflammatory, causing significantly increased production of IL-1, IL-6 and TNF-α at 16:00 and 4:00 hours in all subject groups studied. The proinflammatory cytokines may reduce or even may supress the nocturnal peak of melatonin and the corticosteroids can antagonize this effect by stimulating the production of melatonin (SCHEFF et al., 2010). In a study by Wu and colleagues (2011) in mice with nephropathy, melatonin showed a reduction in the expression of proinflammatory cytokines and increased the expression of cytokines anti-inflammatory such as IL-10, beyond being related to a decrease in oxidative stress and apoptosis. The melatonin has exerted a conflicting effect in the immunoregulation of development Th1/Th2 cell. Thus, melatonin may, possibly, modulate the immune response in manner a dose-dependent.

Disease such as rheumatoid arthritis, can alter the levels of serum melatonin, a study conducted by Cutolo and colleagues (2005), the levels of this hormone in serum at 20:00 and 08:00 hours were significantly higher than in control groups. These differences were more pronounced in patients over 60 years. This study also reported that patients from northern Europe (place with prolonged winter and less exposure to light) when compared with patients in the South of Europe (Italy), had higher concentrations of melatonin and TNF-α. The increased prevalence of autoimmune diseases such as rheumatoid arthritis, which is observed in Northern Europe can be related, possibly with the immunostimulatory activity of melatonin.

The melatonin, because of its pivotal role in the endogenous clock system, has been largely investigated in depression as well as in bipolar disorders. It has shown chronobiotic properties in both mice and humans, an antidepressant effect of the pineal hormone has been supposed (MONTELEONE et. al., 2011). Dysfunctions neuro-immune-endocrine are founds in patients with depression. In theses, were verified high levels in the circulation of corticosteroids, along with a hyperactivation of the immune system and elevated levels of proinflammatory cytokines, low levels of melatonin in the plasma and urine, and a deregulation of circadian rhythms. Treatment with antidepressants seems correct or, at least, can interfere in those changes (ANTONIOLI et al., 2012).

Other hormones also have immunomodulatory effects, such as: the growth hormone (GH) and prolactin. These form a family of hormones that probably are resulting from the duplication of an ancestral gene, and may also have receptors in common (BOLE-FEYSOT, et al. 1998).

Prolactin is a peptide hormone produced by the anterior pituitary gland that is critical role in lactation (PEEVA et al., 2003). It can also interfere in processes such as reproduction, osmoregulation, and behavior (CHIKANZA, 1999). The prolactin can also be produced by lymphocytes, and both B and T cells express prolactin receptors. This hormone can also contribute to a reduction in negative selection or suppress apoptosis of B cells self-reactive. These findings have suggested that prolactin has immunomodulatory functions (PEEVA et al., 2003). Therefore, physiological disturbances of prolactin have immunological effects important (CHIKANZA, 1999).

Evidence of a proinflammatory and immunostimulatory role of prolactin, has been studied extensively from *in vitro* as well as animal models (KELLEY et al, 2007; MUKHERJEE et al., 2010). One of the most consistent findings from *in vitro* studies is that prolactin antisera blocked a number of immune reactions. This led to the discovery that cells involved with immunity appear capable of producing prolactin and GH, but the physiological significance of these observations have not been explored (GALA, 1991).

The GH and the endogenous hormone which its main function is the postnatal growth. According to Mukherjee and collaborators (2010) the idea that GH may influenced the immune system originated from studies of hypophysectomized animals. However, early data proved inconclusive as to whether GH deficiency actually caused the immune defects in these animals. But later studies have identified the presence of the GH receptor in immune cells, which further supports the hypothesis that GH may possess immunomodulatory effect.

Currently, it is known that GH and prolactin has the ability to enhance the proliferation and differentiation of T cells as well as to promote the activity of cytokines of Th1 profile (LANGE et al., 2011). What causes, possibly, the neutralization of the effects of corticosteroids through this increase in Th1 cell responses induced by prolactin. The cytokines IL-1, IL-2, and IL-6 also stimulate prolactin production, while IFN- γ and endothelin-3 are inhibitory (CHIKANZA, 1999). Study conducted by Peeva and colleagues (2003) suggests that the capacity of immune system response to prolactin is genetically determined and their mechanisms of action at the cellular and molecular were not fully described.

The sex hormones are involved in the regulation of autoimmunity (PEEVA et al., 2003). The prolactin may be related to autoimmune diseases, one hypoprolactinaemia hypoprolactinemia impairs immune function while hyperprolactinemia enhances active systemic lupus erythematosus, Reiter's disease, juvenile and adult rheumatoid arthritis (RA), autoimmune thyroiditis, multiple sclerosis, and cardiac allograft rejection, among others(CHIKANZA, 1999).

The immunestimulating hormones like GH and prolactin as well as immunosuppressive hormones such as cortisol are strongly regulated by sleep. GH and prolactin were identified as important endocrine factors mediating the effects of sleep on the response to vaccination. (LANGE et al., 2011). The sleep induced increase in prolactin and GH in combination with

the circadian nadir of cortisol during early sleep in humans are of sufficient amplitude to explain an increase in Th1 cytokine activity during this period (DIMITROV et. al., 2004).

The analyses carried out by Lange and colleagues (2011) suggest that GH, prolactin, and cortisol synergistically contribute to the sleep-dependent enhancement of the vaccination response. They found that GH, prolactin, and cortisol, significantly, contributed to the cell response T helper antigen specific to the hepatitis A virus. The immunoregulatory functions of sleep are not well understood. According to these authors to compare the immune response after Hepatitis A vaccination in healthy men who either slept or stayed awake in the night following inoculations, they showed that sleep acts like an adjuvant to enhance the T helper response antigen-specific and the antibody response. Their data suggest that to sleep as well as the sleep-induced temporary increase in proinflammatory cytokine and hormone activity as possible tools for optimizing vaccination strategies.

The sex hormones also have effects on the immune response, as happens with the estrogen, progesterone and testosterone. These hormones regulate the growth, differentiation, survival and function of many cell types involved in homeostasis and immunity. They exhibit an important role as modulators of the immune system during helminth infections. But also have a direct effect on the helminthes, that may probably be mediated by specific receptors on these parasites (HERNÁNDEZ-BELLO et al., 2012).

The progesterone and estrogen does not necessarily modulate the immune functions similarly. There are many examples in that the effects of progesterone and estrogen are opposed to each other, moreover, their effects on specific organs as well in the immune system may be interdependent (HUGHES, 2012). But, usually the estrogens have stimulatory action on humoral immunity and the progesterone may be a natural immune-suppressors agent (CUTOLO et al., 2006).

There is still an unresolved paradox with respect to the immunomodulating role of estrogens. The estrogens have an activity anti-inflammatory, but can also have proinflammatory role depending on the stimulating factors. On one side, recognizes inhibition of bone resorption and suppression of inflammation. On the other hand, perceive a role of estrogens in immunosupportive role of estrogens in trauma/sepsis and the proinflammatory effects in some chronic autoimmune diseases in humans (STRAUB, 2007).

The estrogens can modulate proinflammatory cytokine release from activated monocytes and/or macrophages. The macrophages release cytokines such as TNF-α, IL-1 and IL6, that may be involved with some symptoms of rheumatoid arthritis, and the release of these cytokines can be modulated by estrogen by different ways (CUTOLO et al., 2006).

There is strong evidence that the estrogens have influence on the development and maintenance of thymic function and, thus, on generation of naive CD4+ and CD8+ T cells. The effects of estrogens on Th17 cells or IL-17 secretion no have been described. Possibly an influence of estrogens on Th17 cells is deduced from estrogens effects on other T cell cytokines. The estrogen may stimulate or inhibit the secretion of IL-6 and also the effect on IFN-γ are heterogeneous. The 17-β estradiol stimulates release of IFN-γ from T cells, but inhibits IFN-γ of macrophages and dendritic cells. This separation may be important because many different effects of estrogens are expected depending on the immune cell involved (STRAUB, 2007).

The progesterone through a variety of mechanisms is required for normal function at multiple stages of mammalian reproduction, such as: oocyte maturation, differentiation of the endometrium, implantation of the embryo, growth of the placenta, quiescence of uterine muscle during fetal development and differentiation of mammary gland tissues (HUGHES, 2012).

In investigation about the potential immunomodulatory properties of dydrogesterone (a progesterone similar to the endogenous) showed that synthetic progesterone, *in vitro*, significantly reduces the levels of the Th1 cytokines, IFN-γ and TNF-α, and increases the levels of IL-4 and IL-6, but IL-10 production was unaffected (RAGHUPATHY et al., 2005).

There are various immune system cells have receptors for progesterone, among them are: granulocytes (mast cells, eosinophils, neutrophils), natural killer cells, macrophages, dendritic cells, T cells CD4 + and CD8 +, furthermore of B lymphocytes. In all these cells the progesterone may cause different effects, inhibit or release granules and/or cytokines, decrease apoptosis, among other (HUGHES, 2012).

Another important role of progesterone is during pregnancy, in this period changes in the immune system are in part modulated by hormonal fluctuations. The progesterone is associated with altered in B cell that secrete immunoglobulins, inhibition of natural killer

cells, and induce a balance between Th1 (proinflammatory) and Th-2 cytokine profile (non-inflammatory) existing in immune responses in pregnant female mammals (DRUCKMANN & DRUCKMANN, 2005). The progesterone which has anti-inflammatory and immunosuppressive properties (STITES et al. 1983), propitiate the development of human T cells producing Th2 cytokines(PICCINNI et al, 2012). The dydrogesterone, with similar action the endogenous progesterone, also has a important role in cytokines regulation of Th1 and Th2 profile, resulting in a reduction of the Th1 polarization and increasing Th2 (RAGHUPATHY et al., 2005). At pregnancy levels, the progesterone also may suppress disease activity in rheumatoid arthritis and multiple sclerosis via inhibition of T helper type 1 and Th17 pathways and induction of anti-inflammatory molecules (HUGHES, 2012).

Androgen hormones such as testosterone can reduce the functions of the immune system, including the production of cytokines. However, the precise role of testosterone in the regulation of immune function remains contentious, the demonstration that testosterone can modulate the expression of a key receptor for danger signals *in vitro* and in immune-competent animals may represent an important mechanism underlying the immunosuppressive effects of testosterone(RETTEW et al., 2008).

Understand the relationship between the endogenous hormones, their temporal variations, and the various interactions that occur, such as hormone-hormone interactions, as well as interactions between hormones and the immune system allows the development of studies that point, according to Kelley and colleagues (2007), to the clinical importance of simultaneous costimulation of cells with hormones and cytokines, as normally occurs in animals and humans.

Prospects to new research

Understanding of the rhythmicity of biological systems is a field of major considerations. Through these knowledge new applicabilities involving the nature of an immune response and new therapies may be proposed. The strategy of chronotherapy is intended to provide the amount of medication required in appropriate times, in order to minimize the toxicity and / or enhance efficacy. Strategy that has been largely benefited from the development of programmed release system. Clinical trials with cyclosporine (immunosuppressive drug) and interferon-α (immunostimulant) confirm the promises that such approaches can optimize the actions toward chronotherapy of the immune system (LÉVI et al. 1992). In carcinogenic drugs, for example the toxicity and anti-carcinogenic activity these, can be significantly

modified by the time of administration. Consider the circadian timer at all stages of development of new anti-carcinogenic drug would possibly, a optimization in therapeutic index for new medicines and benefits for each patient individually taking into consideration their chronobiology (INNOMINATO et al, 2010). In addition to new forms of release of drugs, study involving the chronoimmunology also enables new approaches involving the pathological processes.

It is important to have a wide field of vision, understand that many of the diseases that were previously taken only as of neuroendocrine origin, may also have their origin in disorders of the immune system. When we look at on this perspective, we open new doors to new treatments and possible cures we make room for a field of therapies involving concepts chronoimmunomodulation. According to Monteleone and colleagues (2011) the delays, advancements or desynchronization of circadian rhythms and their relationship with the pathophysiology of psychiatric disorders is also an interesting field of research.

A disruption in the circadian rhythm may cause effects on the neuro-immune-endocrine system. According to Castanon-Cervantes and collaborators (2010) a rupture of the biological rhythm possibly leads to deregulation of the immune system. These chronobiological disorders may occur, for example in shifts work (FRANÇA et al. 2011b) and lead to deregulation of circadian rhythms and even present a higher risk of inflammatory processes (CASTANON-CERVANTES, 2010). Many biological components that regulate the result of the inflammation are regulating circadian. This relationship can be of particular importance for the understanding of the effects of chronic stress and can lead to clinical treatments optimized (SCHEFF et al, 2010).

According with Petrovsky and Harrison (1998) the response to vaccination, for example, may be modified by the time. This raises the possibility that immune responses could be therapeutically manipulated by co-administration of immuno-regulatory hormones such as glucocorticoids. Research on the interactions that occur between hormones and their effects on the immune system are fundamental for further clarification. According to Kelley and colleagues (2007), for example, protein hormones may counteract the catabolic effects of glucocorticoids, but glucocorticoids are likely to impair the actions of GH, and prolactin. As well as, research involving temporal fluctuations which occurs mainly with the sex hormones and their interaction with the immune system is also essential. Epidemiologic, observational

and experimental evidence strongly suggest sex steroids are important modulators of genetic risk in human autoimmune (HUGHES, 2012).

The estrogens are one of the risk factors in autoimmunity. Changes in serum estrogen were found during pregnancy in patients with systemic lupus erythematosus and correlate with changes in cytokines (DORIA, 2004). Progesterone also has effects on the development of diseases autoimmune such as systemic lupus erythematosus. It may have distinct function to estrogen, as this can promote it, the progesterone in some situations can inhibit it (HUGHES, 2012). These data further suggest caution in exogenous estrogen administration, for examples oral contraceptive pills, in patients with autoimmune diseases, but offer the prospect of novel and improved applications of hormonal or/and antihormonal immunotherapy (CUTOLO et al., 2006).

We must not forget to special situations that involve the interaction between the immune system of mother and child, as in pregnancy and during breastfeeding. Research in this field favor explanations that can lead to improvements in the health of mother and child and even reduce the risk of miscarriages and malformations.

In gestation, cytokines such as IFN-γ and TNF-α may cause fetal damage, through activation of activity of the cells natural killer and macrophages (RAGHUPATHY et al., 2005). The balance of Th1/Th2 cytokines favoring a reduction of Th1 cytokines profile that increase the chances of a successful pregnancy (SYKES et al., 2012). But there are many factors that can alter this balance, studies involving congenital infections also need to be developed. In cases of infection, as with *Toxoplasma gondii*, which causes congenital toxoplasmosis, can lead to fetal damage and even miscarriage. Studies in mice infected by this parasite suggests that the loss of embryos found, were associated with a reduction between the regulatory T-cells, which are important for maintenance of pregnancy, and the Th17 cells profile, which release pro-inflammatory cytokines (ROBERT-GANGNEUX et al., 2011).

It is important to emphasize that after birth, the milk, through the activation of phagocytes, presents a probable mechanism of additional protection for infants against infections during this phase of life (FRANÇA et al., 2011a). It also, through its constituents, has the capacity to modulate the immune system of the baby. Shows much potential for improving the immune system as to suppress its activity (CROSS & GILL, 2000). Studies have shown that human

milk cells produce various cytokines, they not only influence the immune system of the newborn, but also are essential for its proper development (DAHGERN et al. 2001).

New observations should be made, understand the hormones and cytokines profile released in milk, and their immunomodulatory activities, taking into consideration a temporal analysis, may allow the breast milk is seen as a natural alternative to a possible treatment for children with diseases. As well as, new research involving the placenta role, the balance of the T helper cells profiles that occur during pregnancy, hormones, seasonal variations and other immunological components that can affect pregnancy, are essential for further clarifications on the immunity maternal-child. This way, they can contribute to society with a reduction of possible pathologies and miscarriage and even bring new perspectives of treatments of congenital disorders and diseases that commonly affect children. This is a diverse field of study and new investigations involving chronoimmunomodulation need be further exploited.

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