(REVIEW ARTICLE)

Alpha-fetoprotein: Immunomodulation in autoimmune diseases during pregnancy and puerperium stages

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Abstract

Alpha-fetoprotein (AFP) has long been associated with regulation and modulation of the immune system in a variety of mammals. In the last several decades, AFP has been linked to autoimmune diseases (ADs) during both pregnancy and in non-gestational disorders via an immunomodulatory function. The course of ADs are highly influenced by soluble factors such as cytokines, chemokines, interleukins, hormones, kinins, growth factors, proteins such as AFP, and various T-cells generated from the immune response. Such factors appear to serve as protective or ameliorating agents during the induction effector stages of the immune response. Immunomodulatory activities of AFP are known to affect: 1) induction of T-cell suppressor activity; 2) down-regulating dendritic-like cell antigen expression; and 3) impairing the function of macrophages and T-cells. Some factors may even be involved in blocking the rejection of the embryo/fetus as an allograft in the mother at the initiation of pregnancy. Thus, the present report reviews the immunomodulation function of AFP during the course of autoimmune disease utilizing AD disorders such as: myasthenia gravis, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, autoimmune liver disorders, diabetes, thyroiditis, and others.

Keywords: Alpha-fetoprotein autoimmune diseases cytokines; Chemokines; Myasthenia gravis; Multiple sclerosis, Pregnancy; Rheumatoid arthritis

1. Introduction

1.1. Historical

An autoimmune disease (AD) is a disorder in which the body's own immune system attacks healthy cells by mistake. Many ADs are not lethal and can co-exist with other autoimmune disorders. The ADs can express a range of disorders from organ-specific (thyroiditis) to systemic types (Lupus) with multi-organ involvement (1, 2). The more common types of ADs include: 1) rheumatoid arthritis; 2) multiple sclerosis; 3) myasthenia gravis; 4) lupus erythematosus; 5) Hashimoto's disease; 6) Grave's Disease; and many others shown as in Table-1.

The pathological course of ADs are highly influenced by factors such as hormones, cytokines, growth factors, chemokines, kinins, interleukins, and effector T-cells generated by the immune response (3, 4). Some ADs exhibit remissions in the second and third semesters of pregnancy and in the post-partum period. In this regard, it has been proposed that maternal and placental proteins and associated soluble factors serve as protective and immunosuppressant agents at the induction and activation stages of the immune system in response to embryonic and fetal cells and their protein secretions (2-4). Some plausible immunosuppressive factors could include pregnancy

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associated glycoproteins such as alpha-fetoprotein, human chorionic gonadotrophin, and pregnancy associated protein-A. The mechanism of why the fetus is not subject to rejection as an allograft is not fully understood, however it might be associated with the induction of the soluble immunosuppressive factors (i.e. AFP) which could produce an immunotolerant state at the maternal/placental interface.

1.2. Alpha-fetoprotein and Immunomodulation

Human alpha-fetoprotein (AFP) is a tumor-associated 69kD fetal glycoprotein that regulates growth both in the fetus and in juvenile/adult tumors (5). AFP is first secreted by the yolk sac and then by the fetal liver during pregnancy; however, AFP can be re-expressed in adult life in cancers such as: hepatomas, germ cell tumors, yolk sac tumors of the ovary, and gastrointestinal cancers (6). In the clinic, AFP been utilized both as a tumor biomarker and as a gestational age-dependent fetal defect screening agent. AFP is classified as a member of the albuminoid gene family and exhibits a 3-domain single chain glycoprotein containing 3-5% carbohydrate (glycans) chains (7).

Alpha-fetoprotein (AFP) is an oncofetal biomarker also known to function as an immunomodulatory agent. Human AFP has been shown to suppress the mitogenic stimulatory response produced by various lectins as well as inhibiting the mixed leukocyte reaction (MLR) by inducing the production of suppressor T-cells (8, 9). It was further demonstrated that AFP could suppress Class-II major histocompatibility complex (MHC) protein expression on macrophages, which may allow the fetus to acquire tolerance to self-antigens during in utero development. AFP has also been implicated in the blocking of Class II MHC antigen expression by human myelocyte macrophages (10). Recent studies have shown that AFP can inhibit natural killer and suppressor cell activity (24) and enhance cytokine, chemokine, and growth factor activity (25). It was further demonstrated that AFP can: 1) shield target (hepatoma) cells from TNF-alpha induced apoptosis (11-13); 2) protect such cells from cytotoxic lymphocyte attack; and 3) block progression of the caspase apoptotic pathway (14-16).

Objective and Aims

The present review and update was intended to survey and elucidate the relationship and immune connection between AFP and ADs that has been revealed over the last four decades. Thus, the first objective of the present treatise was to seek out experimental and clinical examples of AD treatment outcomes in pregnant animals and human patients exhibiting aberrant AFP levels. A second objective was to determine whether such AFP levels correlated with increased production of immune system-derived cells and secreted humoral factors. Such factors might serve as causative agents of immunosuppression, immunomodulation, or immunotolerance (17). The third aim was to examine whether AFP could influence the course of autoimmune disease by ameliorating, and possibly correlating with the course of clinical treatment and outcome. Finally, the aim was to search and enumerate whether AFP-generated immune soluble factors might occur coincident with the remission or relapse of the autoimmune disease in pregnancy. Thus, the present report attempts to shed light on whether the aberrant serum AFP levels and induced soluble factors during pregnancy and puerperium stages could contribute to the amelioration observed in reducing AD manifestation during pregnancy and in the puerperium. Finally, it should be noted that this report will only discuss published papers regarding AFP and associated ADs, even though many more ADs are known to exist (see Table-1).

2. Material and methods

2.1. Alpha-fetoprotein and Selected Autoimmune Diseases

Much literature has been generated regarding the role of alpha-fetoprotein in ADs such as multiple Sclerosis (MS), myasthenia gravis (MG), and rheumatoid arthritis; however, somewhat less AFP literature has been published involving ADs such as thyroiditis, diabetes, Sjogren's Syndrome, and autoimmune liver diseases (such as hepatitis and primary biliary cirrhosis) (2, 18) Hence, these latter ADs will be denoted and discussed in the present review.

2.1.1. AFP Effects on Myasthenia Gravis

Myasthenia Gravis (MG) disease is a chronic autoimmune-mediated neuromuscular transmission disorder acquired during late teenage and young adulthood (3). Most patients have onset of disease between the ages of 20 and 30 years of age. At least 30-40 cases per million people worldwide have an acquired MG (4). Similar to other ADs, this neuroinflammatory disease is two times more prevalent in women than in men (1). The majority of women with MG are of child-bearing age and are diagnosed in 1 in 20,000 pregnancies. MG is a chronic neuromuscular transmission disorder which manifests in skeletal but not smooth muscles and induces muscular weakness and fatigue (5). Autoimmune antibodies are produced against the nicotinic acetylcholine receptor (AchR) located at the neuromuscular junction (19). The disease is highly influenced during pregnancy by hormonal factors, and anti-inflammatory agents

which appear to serve as neuroprotective factors in the immune responses directed against this neuromuscular disease (20). Thus, changes in circulating pregnancy hormones and soluble protein factors such as AFP are thought to bestow immuno-protective effects upon the neuromuscular junction receptor which is the causative factor in the pathology of MG (21).

From 1979 to 1984 and beyond , the Israeli research team of Abramsky and Brenner discovered an association of AFP with MG (22-25). As discussed above, MG is an autoimmune disease resulting from the effect of specific antibodies directed against the acetylcholine receptor (AchR) located at the neuromuscular junction. Anti-AchR antibodies have been demonstrated in serum and histochemically at the neuromuscular junction of many MG patients (26-28). Clinical and pathological features of MG can be mimicked and produced in laboratory animals by passive transfer of anti-AchR antibodies from MG patients to rabbits or animals with experimentally induced MG (29, 30). Thus, Neonatal MG can also occur by passive transfer of anti-AchR IgG antibodies from mother to the newborn infant (26-28). The Israeli team further examined the effect of AFP derived from amniotic fluid on the development of experimental allergic MG in rats (25). These researchers employed both in vitro and in vivo experiments to demonstrate that purified AFP inhibited the binding of antibodies to the AchR by the direct interfering action of AFP on the antibodies via a non-specific binding interaction (20, 23).

The inhibitory action of AFP has been proposed to explain the MG remissions in women in the second and third semesters of pregnancy and in neonates , in contrast to relapse episodes of postpartum patients.(30-32). Such postpartum relapse events have also been reported in other ADs such as rheumatoid arthritis and system lupus erythematosus, and in graft rejection during pregnancy (33). In further studies, the Israeli team demonstrated that autoimmune MG could be prevented in rats immunized with purified Torpedo (eel) AchR extracts and treated with purified AFP and AFP-enriched fractions (23, 25). Finally, myasthenic crises have been reported in women in the puerperium period, but not in their offspring displaying high AFP levels at birth (28).

2.1.2. AFP Effects on Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune-mediated neurological disorder with antibody directed against the myelin sheath of nerve cells. It is acquired during young adulthood and most patients' manifest onset of disease between the ages of 20 to 30 years of age (1, 34). At least 400,000 people in the United States and 1 to 2 million people worldwide have MS (1, 4). This autoimmune neuroinflammatory disease is three times more prevalent in women than in men (2). The majority of women with MS are of child-bearing age; hence, its occurrence in pregnancy is more commonly reported (4, 36). MS is the most prevalent de-myelinating disease of the central nervous system (CNS) and is both an unpredictable and a potentially disabling condition (3). No single gene or gene cluster is known to produce multiple sclerosis. The disease is highly influenced during pregnancy by hormonal factors, and anti-inflammatory agents which are thought to function as neuroprotection factors in the immune induction and effector stages of this neurological disease (34, 35). Changes in circulating pregnancy hormones and soluble circulating factors (steroids, hCG, AFP etc.) have further been proposed to provide protective effects against the immunoneurological damage that underlies MS pathology (37).

During pregnancy, MS activity produces two major manifestations, a period of profound reduction of MS symptoms (remission) in the third trimester followed by an exacerbation of disease (relapses) in the postpartum period prior to returning to the mother's pre-pregnancy disease state (38). Past and present data support the conclusion that progression of MS is not worsened, but may actually be lessened or reduced during MS pregnancy. In a study of 935 pregnant women with MS, relapses occurred in 40-50% during the postpartum period, while only 10% relapses occurred in the second and third trimesters (40 (36). Investigators found a notable reduction of relapses in the third trimester of pregnancy, but a high increase of relapses in the first 3 months following delivery (28,35 37). Thus, there appears to be soluble immune-protective factors (i.e. AFP) produced during pregnancy that cause the MS disease to be less active. As discussed above, such soluble factors may be capable of suppressing cell-mediated immune responses (see below and Table-2 for such factors).

The early studies of MS and AFP can be attributed to the meticulous research by the Israeli team of Obamsky and Brenner from 1982 to 2009 (38-47). Studies were done using an animal model of MS termed "experimental allergic encephalomyelitis (EAE)" induced in guinea pigs and rabbits by immunization with myelin basis protein (MBP) (40, 41). Daily administration of AFP was employed which demonstrated inhibition of both the cell mediated immune response to MBP and the binding of MBP antibody to its antigen (39). In the following year, this same scientist team reported human pregnancy-derived AFP was capable of delaying rabbit EAE (MS) which only occurred following delivery or fetal absorption (1940).

In 1985, these same Israeli scientists showed that purified AFP (50 μg) was able to suppress rabbit EAE following the onset of neurological signs and that AFP improved the clinical scores of the affected animals (41). These researchers reported that pregnancy (via AFP) protected the animals from developing EAE by induction and altercations in their host immune systems as long as AFP was present in the postpartum and neonatal stages (38, 42). MS is an unpredictable, disabling condition in humans; hence, the amelioration of MS symptoms during pregnancy is highly indicative that soluble factors, such as AFP and other immune factors cause the disease to be less severe (35-37). A clinical case report of a pregnant woman with reduced functional muscle strength added credence to the immuno-protective role of AFP in MS (38, 42, 46-47).

2.1.3. AFP Effects on Rheumatoid Arthritis

Rheumatoid Arthritis is an autoimmune disease that results in a chronic, systemic disorder affecting many tissues and organs, especially flexible synovial joints (1, 4). Disorders that mostly affect joints and muscles are grouped as the autoimmune rheumatic diseases, and include the following: rheumatoid arthritis, systemic lupus erythematosus, primary Sjogren syndrome, systemic sclerosis (scleroderma), and idiopathic inflammatory myositis (3). If not treated, RA leads to disabling and painful conditions which cause substantial loss of function and mobility at the target tissue (i.e., synovial joints, etc). Pathology of the disease process encompasses destruction of articular cartilage and ankylosis (fusion) of the joints. However, RA can also cause diffuse inflammation within the lungs and membranes surrounding the heart (pericardium), membranes of the lungs (pleura), the white of the eyes (sclera), and various nodule lesions in subcutaneous tissues (3, 4).

RA is a chronic disease and rare spontaneous remissions may occur; moreover, some of the most striking examples of temporary improvement in disease activity are seen during pregnancy. It has been observed for many years that more than two thirds of patients with RA go into remission during pregnancy; however, the precise cause for this beneficial effect is not fully understood (48). Thus, the mechanism of remission of RA in pregnancy is incompletely known and has been proposed as an induction of an immunosuppressive state in the womb caused by soluble immunoprotective factors such as AFP and others. The most likely explanation was that soluble factors may have caused the release of lymphokines/cytokines/interferons (see Table-2) which had an immunosuppressive effect on the course of rheumatoid inflammation. In following years, a case report was issued stating that an RA-affected woman's serum AFP levels were 3 times the median for her pregnancy at 15 weeks, and a subsequent AFP determination at 16 weeks gestation (49). Her AFP amniotic fluid level was borderline elevated, and she gave birth to a normal male infant at 39 weeks. Finally, a subsequent clinical study in Europe determined that measurements of serum levels of both trophoblast-specific Beta-1 globulin and AFP in pregnant women with rheumatoid arthritis had a notable value in determining the course of disease treatment (50).

In subsequent years, the purification and production of a recombinant form of human AFP (ReAFP) were developed and utilized. The methodologies of ReAFP production have been reported in both yeast strains and in infectious baculovirus inoculum optimized for AFP protein yields (51-55). The purification and characterization of recombinant versions of human AFP were further expressed in the milk of transgenic goats which produced high amounts of purified ReAFP (51). These advancements led to subsequent clinical trial utilization of a recombinant form of HAFP code-named "MM-093", an injectable formulation of ReAFP. This preparation form of ReAFP was intended to be used in trial testing for potential treatment of human patients with rheumatoid arthritis, and eventually myasthenia gravis, multiple sclerosis, autoimmune Uveitis, and psoriasis (52-53). These studies led to a randomized, double-blind placebo-controlled clinical trial of the ReAFP (MM-093) in patients with active rheumatoid arthritis (52, 53). Although MM-093 in phase-II trials showed study efficacy and was well tolerated in patients, the study was not approved to advance to phase-III testing. It was proposed that ReAFP failed to achieve phase-III trial approval due to the following several reasons. First, the full-length AFP (69Kd) molecule is bristling with innumerable biologically-active peptide subdomain segments on each of the three domains of the fetal protein. Secondly, some of these peptide sites might be masked, hidden, or not fully exposed until AFP is introduced into differing or highly variable biochemical/biophysical micro-environments (56). Thirdly, stimulation of the biologic response induced by these exposed peptide segments cannot be predicted, limited or controlled. These activated sites might cause or produce undesired and dangerous side effects, such as malignant or inflammatory reactions.

2.1.4. AFP Effects on Systemic Lupus Erythematosus (SLE)

Serum concentrations of AFP in clinical patients with systemic lupus revealed that 20% of such patients showed serum elevated AFP levels ranging from 30-233 ng/ml (57, 58). The serum of such patients showed a significant correlation of elevated AFP together with raised levels of anti-dsDNA antibody, a hallmark biomarker of SLE (59). In an animal model of SLE produced in F1 hybrid NZB/W mice, steroid hormones affected the development of reproductive traits, altered immune responses, and increased the severity of the SLE disease (60). Serum levels of AFP, a protein which bind

estrogens and modulates immune responses, were greater in NZB pregnant females than in control (C57BL/6) mice treated with six various steroid hormone modulators. It was determined that increased AFP levels in the mouse dams influenced severity of disease, increased longevity in the offspring, and affected the course of the SLE disease.

In a subsequent study of human SLE in the clinic, it was demonstrated that AFP levels are increased during pregnancy when compared to control pregnancies (59). The elevated levels of AFP were found to be correlated with high anti-cardiolipin antibodies and with preterm deliveries. Finally, in one case study, a woman was found which had SLE in concordance with the traits of autoimmune hepatitis (61). The patient displayed hyperbilirubinemia, elevated liver function enzymes, raised levels of anti-DNA antibodies, positive anti-nuclear antibodies (ANA), and prominent elevated levels of AFP. Thus SLE disease, co-morbid with autoimmune hepatitis, exhibited elevated AFP in this rare dual clinical presentation. Such findings might be beneficial to clinicians in attempting to identify and treat patients with both diseases (see below).

2.1.5. AFP Effects on Autoimmune Liver Disorders

The autoimmune liver disorders include both autoimmune hepatitis and primary biliary cirrhosis in which both can be associated with the subsequent induction of liver cancer, namely, hepatocellular carcinoma (HCC). Elevated AFP serum levels have been previously reported in two patients originally diagnosed with autoimmune liver disorders, which had progressed to HCC (62). In both cases, AFP was markedly elevated (up to 1,000 ng/mL) with abdominal MRIs exhibiting enlarged liver masses. Such cases highlight the fact that HCC can occur secondary to autoimmune hepatitis and/or primary biliary cirrhosis in the absence of viral hepatitis and excessive alcohol consumption. Predictive factors for HCC associated with autoimmune liver disorders included: 1) elevated AFP; 2) liver cirrhosis; 3) history of blood transfusions; 4) immunosuppressive (corticosteroid) treatment; 5) portal biliary hypertension; 6) thrombocytopenia, and 7) raised prothrombin levels caused by the absence of Vitamin-K-D absence (63, 64). Thus, elevated AFP serum levels exceeding 30-50 ng/ml are observed in autoimmune hepatitis, metastatic liver cancer, and liver cirrhosis. Moreover, AFP serum concentrations were found to be correlated with the severity of liver cirrhosis (65).

Finally, it has been recently reported that AFP can serve as a self-antigen to induce autoantibodies in patients with liver cancer and other hepatic disorders (66). The induction of variant conformational forms of AFP together with exposed occult antigenic determinant sites on the AFP polypeptide can convert the normal tertiary-folded AFP into a disordered protein. Such abnormally-folded proteins can impair central immune tolerance leading to autoantibody production to self-proteins (cryptic epitopes) and sensitized β-lymphocytes. This process also occurs in Battan's disease, a neurodegenerative autoimmune juvenile disease (66).

2.1.6. AFP Effects on Autoimmune Diabetes

It has been reported that pregnant women with insulin-dependent gestational diabetes display an observed decrease in their maternal serum and amniotic fluid AFP levels (67, 68). Although the 10% reduction in AFP levels have yet to be adequately explained, a weak but significant correlation with glycosylated hemoglobin A1C has been reported. Interestingly, the decreased AFP levels did not correlate with fetal growth delay or retardation, or neural tube defects. The 10% correction factor for AFP levels in insulin-dependent diabetes has been in practice in nationwide screening laboratories for many years and only recently has come under scrutiny (69). In the year 2008, a study was conducted to examine whether the 10% correction factor for AFP was required for both type-1 and type-2 diabetic pregnant women 68). Although, both types of diabetic patients were similar in their median AFP levels, they were both significantly lower than controls even after the required 10% correction factor. Thus, both type-1 and type-2 diabetic APF levels need adjustment in order to compare to the nondiabetic pregnant population levels.

2.1.7. AFP Effects on Autoimmune Thyroiditis and Inflammatory Bowel Disease

In one study, experimental autoimmune thyroiditis was induced in transgenic mice which were capable of synthesizing human AFP (76). Such mice developed thyroiditis mimicking the human disease including the mononuclear immune cell infiltration and migration into the thyroid gland follicles. The transgenic mice, which exhibited high levels of AFP, were significantly immunosuppressed in autoimmune disease development which was accompanied by mononuclear cell infiltrates. The results in the transgenic mice with induced thyroiditis further showed highly reduced numbers of CD4+ and CD8+ splenocytes, total thymocytes, and CD4+ thymocytes as compared to control mice. Their results clearly demonstrated that ubiquitously produced AFP modulated in vivo T-cell development and T-cell immune responses. In addition, clinical patients exhibiting nodular Hashimoto's Disease that were positive for autoimmune thyroid antibodies, also displayed clinical signs of ataxia telangiectasia (AT) (71). This AT disease is characterized by high AFP levels and neurological manifestations, infections, and cancers. In addition to these clinical features, thyroid autoantibodies have been known to associate with other autoimmune diseases. Thus, other different autoimmune

diseases have been known to co-exist in patients with AT disease, a non-autoimmune genetic disorder. In this situation, AT disease is known to secrete copious amounts of AFP into the serum (72). It is tempting to speculate that serum AFP might be capable of modulating T-cell development and immune responses in these AT patients.

Regarding inflammatory bowel disorder, it would further seem prudent to discuss clinical examples of gut-related autoimmune diseases in pregnant women with immune-mediated inflammation. Such studies in pregnant and postpartum women with inflammatory bowel disease (IBD) have been addressed and reported (73-75). In these studies, the role of AFP as an immunoregulatory agent was described as; 1) inducing T-cell suppressor activity; 2) down-regulating dendritic-like cell antigen expression and 3) impairing the function of macrophages. These observations and reports regarding pregnant women with IBD described potential correlations between AFP expression and disease activity during different stages of pregnancy and postpartum (74, 75).

2.1.8. AFP Effects on Autoimmune Sjögrens Syndrome

It has been reported that a female patient with Sjogren's syndrome, an autoimmune disease, exhibited extremely elevated AFP levels (1, 210 µg/mL) when treated with immunosuppressant agents (76). This patient proved negative for liver cancer but was positive for anti-nuclear (DNA) antibodies and other liver disorders consisting of cysts, gall bladder damage, and jaundice. A second patient with Sjorgrens Syndrome together with autoimmune hepatitis demonstrated that high AFP levels were caused by an underlying autoimmune liver disease (77). Finally, a third patient (elderly female) with Sjorgren syndrome was found to have mild liver damage together with elevated AFP serum levels. However, a CT scan later revealed she had hepatocellular carcinoma (ACC) suggesting that patients with primary Sjorgren's syndrome might be candidates for liver cancer outcomes (78)

3. Results and discussion

3.1. Additional and concluding remarks

AFP and autoimmune disease inflammation has been long reported to be present during pregnancy. As shown above in this report, AFP was found to be associated with myasthenia gravis and multiple sclerosis remission with AFP playing a protective role during such pregnancies. As previously discussed, studies pioneered by Abramsky and Brenner (71) demonstrated that AFP was one of the major soluble factors produced during pregnancy that caused immunosuppression in MG patients by competitive inhibition of autoantibody binding to the acetylcholine receptor (22). Subsequently, AFP in pregnancy was demonstrated to suppress immune EAE by decreasing the antibody levels produced against myelin basic protein in EAE patients with subsequent amelioration of immune-associated interactions (36, 38, 39).

Using recombinant human AFP (ReAFP) in animal models of EAE, ReAFP markedly improved the clinical manifestation of animal EAE by preventing CNS inflammation and axonal degeneration (41, 40, 43). In a prior study, T-cells from AFP-treated mice significantly reduced immune activity toward the myelin sheath oligodendrocyte glycoprotein (MOG), a MS mediator and antigen (39). These mice exhibited less T-cell proliferation and reduced THI cytokine secretion. In addition, AFP affected the humoral immune response in the mice and caused in inhibition in MOG-specific antibody production. The expression of DB11 to the MHC Class II protein and chemokine receptor CCR5 in these mice exhibited down-regulation of both monocytes and macrophages. In all such studies, AFP served to decrease various aspects of neuroinflammation of MS including: disease severity, axonal loss and damage T-cell reactivity, and antigen presentation (38, 39). In subsequent experiments by the same investigators, the immunomodulation of EAE by AFP was associated with elevation of immune cell apoptosis and increased levels of transcription factor Fox P3. AFP was found to increase the expression of the pro-apoptotic factors BaX,, Bid ,and others in peripheral lymphocytes. This increase was accompanied by a raised expression of transcription Factor FOX P3 in lymph node cells as well as accumulation of DC4+ FOX P3+ regulatory T-cells in the CNS (39, 40).

A study of autoimmune inflammation in knee joint-induced arthritis induced in transgenic mice revealed that the animals were secreting and producing 20 µg/mL of AFP in their serum (41). AFP was found to be instrumental in suppression of induced autoimmune arthritis in the transgenic mouse model and functioned as an immunosuppressant agent that ameliorated the development of this inflammatory knee-joint autoimmune disease. Serum AFP levels were 500 times higher in the transgenic mice than in the blood of control mice (43).

Inflammation can also precede to disease states such as autoimmunity. During inflammation in animal pregnancies, AFP has been reported to interact and bind to caspase-3,9 enzymes (cysteine proteases) which constitute the key components of molecular complexes called inflammasomes; these are inflammation-induced intracellular organelles

(34, 79). It has been reported that AFP can serve both as an acute and a chronic phase reactant depending on its developmental stage. AFP functions as a positive acute phase reactant in the embryo, fetus, and placenta during pregnancy, and as a negative acute phase protein in the postnatal and adult period of life (42, 81). Finally, it has been reported that AFP is also a modulator of the pro-inflammatory response of human keratinocyte event during development in human skin (2009). In that report, AFP was shown to enhance the baseline expression of cytokines, chemokines, and growth factors. Thus, AFP dose-dependently increased levels of tumor-necrosis factor alpha (TNFα), granulocyte macrophage colony stimulating factor (GMSF), and interleukin-8 (IL-8) in keratinocyte pro-inflammatory events.

Lastly, it is believed that the pathogenic mechanisms of ADs in the non-pregnant population are a consequence of activated immune processes, in contrast to the pregnant state which invokes the emergence of systemic immunosuppressive factors within the mother (2). Such soluble factors produced by the mother, fetus, and placenta are thought to play major roles in retaining the fetus as an allograft within the mother. It is tempting to speculate that these soluble factors produce immunomodulatory agents in excess at the fetoplacental interface that could aid in preventing fetal-host rejection (17).

Table 1 Selected autoimmune diseases are listed below according to their common occurrence, rarity, potential fatality, and involvement. It is believed that at least 80 different autoimmune diseases exist

Sr. No.	Autoimmune Diseases
1.	**Common Autoimmune Diseases**
	• Rheumatoid arthritis – bone/joint nflammation • Hashimoto's disease – Hypothyroid condition • Celiac Disease (Sprue) – gluten sensitivity • Graves' Disease – Hyperthyroid condition • Type-1 Diabetes – low/insulin production • Pernicious Anemia – Vitamin – B12 deficiency • Multiple Sclerosis – nerve de-myelinating disorder • Myasthenia Gravis – antibodies to Ache receptor
2.	**Rare Autoimmune Diseases**
	• Eosinophilic granulomatosis-increased eosinophil production • Guillain-Barre Syndrome-antibodies attacks body nerve networks • Kawasaki Disease – inflammation of blood vessels • Mixed connective tissue disease – form of scleroderma with polymyositis (System Sclerosis) • Paroxysmal nocturnal hemoglobinuria – impaired bone marrow function • Retroperitoneal fibrosis – extensive scar tissue in back of body cavity • POEMS Syndrome – a disease of polyneuropathy tingling, and weakness in limbs
3.	**Potentially Fatal Autoimmune Diseases**
	• Autoimmune Giant Cell Myocarditis – inflammation of the heart muscle • Lupus erythematosus – body attacks tissues of joints skin, brain, lungs, kidneys, DNA, and blood vessels • Autoimmune Vasculitis – narrowing and inflammation of blood vessel walls • Anti-NMDA aspartate receptor encephalitis – inflammation in the brain • Hemolytic anemia – Red blood cells are destroyed faster than replenished • Psoriasis – a dermatitis disease of scaly skin patches

Legend Notes: 1) See above and in the text: multiple sclerosis, rheumatoid arthritis, and type-1 diabetes for fatalities 2) AchdR – acetylcholine receptor nicotinic

Table 2 Selected autoimmune diseases are listed in accordance with their target organ/tissue, physiological impairment, and the soluble immune factors induced

Sl.No.	Autoimmune Disease	Targeted organ, cell or tissue	Physiological effect/impairment	*Soluble immune factors activated
1.	Myasthenia Gravis	Neuromuscular junction of muscle nerve (interface connection)	Skeletal muscle weakness, fatigue, blocked muscle-nerve transmission	CD4, CD8, IL-28, TH-1 lineage, IL-19, IL-20, IL-35 Suppressor factors
2.	Multiple Sclerosis	Myelin sheath of nerve cells, MOG glycoprotein	Impaired, weakened transmission of nerve impulse along axons	Interferon-V, IL-12, Helper (TH) cells, IL-17, IL-1, IL-22, suppressor factors
3.	Rheumatoid arthritis	Flexible synovial joints and muscle pockets (pouches)	Destruction of articular cartilage and ankylosis, fusion of joints	IL-1, IL-17, IL-18, TNF-α, RANKL suppressor factors
4.	Systemic Lupus Erythematosus	Lymphoid tissues, multiple organs, tissues and cells, immunotolerance	Chronic inflammation throughout body, lymphoproliferative tissues, cancers	TNF-α, IL-15, IL-17, IL-21 Interferon-α, TH-1 cells
5.	Type-1 Diabetes	Pancreatic cell Insulin production, regulates blood sugar	Antibody attack on pancreatic-Beta cells, high blood sugar	TH2, TH1 cells, IL-10, IL-33 TGF-Beta
6.	Thyroiditis Hashimoto's	Thyroid follicle cells, attack on Thyroglobulin molecule	Produces Hypothyroidism, lymphocyte infiltration into thyroid gland	Anti-PD-1, CtLA-4, PDGF, IL-6, Interferon
7.	Autoimmune Liver Disorders	Liver, Bile ducts, liver induced hepatitis, primary biliary cirrhosis	Liver portal hypertension, increased prothrombin levels, Vit-D deficiency	IL-8, IL-1, TNF-α, RANTES MCP-1 suppressor factor
8.	Inflammatory bowel disease (ulcerative colitis)	Lining of the mucous membranes of gastrointestinal tract (Crohn's disease)	Chronic bacterial inflammation, abdominal pain, fatigue, bloody stools	TNFα, IL-22, IL-17, IL-5, IL-10, IL-13, IL-1B
9.	Sjogren's Syndrome	Mucous membranes of salivary glands of eyes and mouth	Anti-DNA antibody, liver disorder, dry eye and mouth	IL-17, IL-12, IL-23, IL-4, IL-6, TNF-α MIP-1a, CXCL8

*Alpha-fetoprotein is capable of activity, together with one or more of soluble factors listed (see Ref.# (80) below. Legend: CD4 = Helper T-cell co-receptor; CD8 = cytotoxic T-cell co-receptor; CTLA = immune checkpoint receptor; CXCL8 = IL-8 chemokine; IL = Interleukin family of cytokines; MCP-1 = Monocyte chemo-attractant proteins; MIP-1 = Macrophage Inhibitory Protein; PD-1 = Program Cell death checkpoint; PDGF = Platelet-derived growth factor; RANKL = Apoptosis Regulator Ligand; TGF = transforming growth factor; TH = T-cells with CD4 receptors; TNF-α = tumor necrosis factor alpha

4. Conclusion

From the present review, it can readily be ascertained that AFP is a major immune-associated soluble factor in autoimmune diseases during pregnancy and postpartum stages. The immunomodulatory activities of AFP cited in this report have included:T-cell suppression ,down-regulation of dendritic antigen presentation, impairment of macrophage and T-cell functions, and enhanced expression of cytokines, chemokines, interleukins, interferons, and growth factors. This report will serve to aid and benefit basic researchers, physicians, clinicians, and practitioners in the biomedical community at large.

Compliance with ethical standards

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