More Than a Tumor Marker…A Potential Role for Alpha-Feto Protein in Inflammatory Bowel Disease

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Background: Human alpha-fetoprotein (hAFP) is a glycoprotein derived from the gut entoderm and expressed sequentially by cells of the yolk sac, fetal liver, and gastrointestinal tract. By adulthood, serum levels of alpha-fetoprotein (AFP) are undetectable in healthy, nonpregnant adults. Despite the clinical utilities of AFP monitoring in pregnancy and malignancy, much remains to be determined regarding its potential physiological functions.

Methods: We focused on literature related to AFP's immunoregulatory role and its ability to modulate disease activity both in animal models of autoimmune disorders and in human clinical studies.

Results: Evidence suggests that AFP plays an important role in immunoregulation by inducing T-cell suppressor activity, downregulating dendritic-like cell antigen expression, and impairing the function of macrophages. Studies evaluating AFP and its effects in rodent models of autoimmune diseases have shown that AFP is associated with downregulation of inflammation. Observations in studies of pregnant patients with immune-mediated inflammatory diseases have also described potential correlations between AFP expression and disease activity during different stages of pregnancy and postpartum.

Conclusions: We propose further prospective evaluations of AFP expression during pregnancy in inflammatory bowel disease patients to further correlate with disease activity and consider the potential of AFP as a novel therapeutic agent.

Key Words: alpha-fetoprotein, inflammatory bowel disease, immunoregulation, autoimmune disease, pregnancy

INTRODUCTION

Human alpha-feto protein (hAFP) is a tumor-associated glycoprotein encoded by the *AFP* gene located on the q arm of chromosome 4 (4q25). Alpha-feto protein (AFP) is a single polypeptide chain with a molecular weight of 70,000 derived from gut entoderm and during development is expressed sequentially by cells of the yolk sac, fetal liver, and gastrointestinal tract.[1, 2] AFP is degraded in the liver, with a half-life of 3–4 days in infants and 5–6 days in adults.[3] In adults, hAFP is silenced by methylation, a process where gene transcription is repressed without altering DNA sequences, and re-appears in restorative processes such as hepatic damage and regeneration and during the growth of solid tumors including hepatomas and germ cell cancers.[3, 4] Although little is known regarding the function of AFP, it presumably serves as a transport molecule for several ligands including bilirubin, fatty acids, retinoids, and steroids.[5] Clinically, AFP levels have primarily been used as tumor markers, and during pregnancy to monitor fetal growth and predict adverse outcomes.[6] We suggest a potential immunoregulatory and therapeutic role for AFP and as a possible therapy for inflammatory bowel disease (IBD) and other chronic immune-mediated inflammatory disorders.

ANIMAL STUDIES LOOKING AT AFP'S ROLE IN INFLAMMATION

Alpha feto-protein was first discovered in 1963 by Abelev et al. At that time, AFP (termed "embryonal alpha-globulin") was found to be expressed by hepatomas and in the serum of mice undergoing liver regeneration. The investigators determined that the same protein found in the embryo of mouse serum was also expressed in the liver during proliferation of both normal and malignant cells.[7] These findings have led to the diagnostic utility of AFP as a tumor marker for hepatocellular and germ cell tumors.[3, 4]

The potential immunoregulatory impact of AFP was initially based on the hypothesis that the elevated levels of serum AFP in the developmental embryo could be protective against a maternal immune attack.[8] To determine whether an immunoregulatory effect was associated with amniotic AFP, and not albumin or transferrin, other proteins found in high concentrations in amniotic fluid, Murgita and Tomasi, demonstrated that AFP induced a dose-dependent suppression of spleen cells' antibody response that was abrogated when AFP was depleted from amniotic fluid.[8] The amniotic fluid in mice retained the ability to suppress primary and secondary antibody responses despite removal of albumin and transferrin. Although the mechanism by which AFP induced immunosuppression was

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not determined after accounting for confounding variables, a limitation of the study, the investigators concluded that AFP was the protein responsible for immunosuppression in mouse amniotic fluid.[8]

Subsequently, Crainie et al. attempted to determine AFP's mechanism of action by demonstrating that purified AFP, derived from mouse amniotic fluid, downregulated dendritic-like cell expression and suppressed the ability of lymphokines to stimulate dendritic-like cells' ability to express antigens.[9] One of the main limitations of this study was that the purification method used to prepare AFP resulted in variation in its immunoregulatory function, suggesting that the purification method might have destroyed some of its biological activity.[9] In 2002, a study assessing HIV transmission in pregnancy found that AFP, purified from human pooled cord blood, specifically binds to macrophages and impairs macrophage antigen-presenting abilities by blocking high- and low-affinity T-cell binding sites.[10] Along with animal studies, there have been several studies evaluating AFP's role in immunoregulation both in the context of malignancy, such as hepatocellular carcinoma (HCC), and in noncancer study designs (Table 1). Together, these studies suggest a potential role for AFP in inflammation as an endogenous immunomodulator.

DISEASE ACTIVITY DURING PREGNANCY OF IMMUNE-MEDIATED INFLAMMATORY DISEASES

It has long been established that proportions of patients with immune-mediated inflammatory diseases (eg, rheumatoid arthritis, systemic lupus erythematous, multiple sclerosis, myasthenia gravis, and inflammatory bowel disease) experience clinical remission during the second and third trimesters of pregnancy.[20] This period of time correlates with the highest levels of AFP expressed during pregnancy. Proportions of women with myasthenia gravis have less muscle weakness during the second and third trimesters of pregnancy and tend to suffer more postpartum exacerbations (when AFP levels drop dramatically).[21] Similarly, women with rheumatoid arthritis and systemic lupus erythematosus more often have quiescent disease during pregnancy than postpartum.[22]

TABLE 1. AFP and Immunoregulation

Authors	Study Design (Cancer vs Noncancer)	Conclusions
Czokalo M, Wisniewski L (1979)[11]	Noncancer	• AFP in elevated concentrations (4–12 mcg/mL) inhibits both blastic transformation and immunoglobulin release in lymphocyte cultures • AFP plays an important immunoregulatory role during fetal development
Wang W, Alpert E (1995)[12]	Noncancer	• Human AFP-downregulated phorbol 12-myristate 13-acetate induced tumor necrosis factor–alpha (TNF-a) and interleukin (IL)-1B production through a prostaglandin E2–dependent mechanism
Semeniuk DJ, Boismenu R, Tam J, et al. (1995)[13]	Noncancer	• AFP-mediated immunoregulation is an intrinsic property to the molecule itself • AFP-mediated immunoregulation cannot be attributed to its glycosylation or sialylation or the moieties bound to it
Dudich E, Semenkova I, Dudich I, et al. (1999)[14]	Cancer	• AFP can be considered as a highly selective tumor-suppressive factor • AFP can target tumor cells and induce apoptosis through caspase-3-like proteases • AFP can simultaneously be completely nontoxic for normal cells
Um SH, Mulhall C, Alisa A, et al. (2004)[15]	Cancer	• AFP induces the apoptosis of dendritic cells and impairs their function • Patients with HCC and high levels of AFP have decreased ability to produce inflammatory cytokines via antigen-presenting cells
Alisa A, Boswell S, Pathan AA, et al. (2008)[16]	Cancer	• AFP may lead to evasion of tumor control by activating the expansion of inducible transforming growth factor (TGF-B)–producing regulatory T cells
Yang X, Zhang Y, Zhang L, et al. (2008)[17]	Cancer	• AFP may function to inhibit apoptosis and stimulate hepatoma growth through the p53/Bax/ cytochrome c/caspase-3 pathway in the HCC cell line Huh7
Yamamoto M, Tatsumi T, Miyagi T, et al. (2011)[18]	Cancer	• AFP inhbited dendritic cell maturation and IL-12 production from dendritic cells, leading to the impairment of natural killer (NK) cells' cytotoxic activity • AFP might affect the immune surveillance of innate immunity in HCC patients by inhibiting NK activity, leading to the promotion of HCC development
Yang X, Chen L, Liang Y, et al. (2018)[19]	Cancer	• AFP was shown to:oinhibit cell proliferationoincrease the number of cells undergoing early apoptosisoarrest the cell cycle in HepG2 cells through the TGF-B and p53/Bax/Caspase-3 signaling pathways • AFP should be further investigated as a novel approach to HCC treatment

Studies assessing remissions during pregnancy in rheumatoid arthritis (RA), multiple sclerosis (MS), and systemic sclerosis have found that human leukocyte antigen (HLA) discrepancy between mother and fetus contributes to this phenomenon.[23–25] Subsequently, Kane et al. evaluated pregnancies in women with ulcerative colitis and Crohn's disease to determine whether maternal-fetal HLA discrepancies would similarly impact disease activity during pregnancy and postpartum.[26] They confirmed that maternal–fetal HLA discordance correlated with the increased rates of remission seen in IBD patients during pregnancy compared with women and fetuses concordant for Class I and II HLAs, both between women and in the same mother with different pregnancies.[26] A specific downregulatory mechanism remained to be determined.

Most exacerbations of IBD in pregnancy occur during the first trimester or postpartum, when AFP levels are at their lowest.[27] In 2013, the first large-scale study prospectively following 209 women with either ulcerative colitis (UC) or Crohn's disease (CD) during pregnancy found that most relapses in UC occurred during the first and second trimester and postpartum, whereas pregnant CD patients did not experience disease activity differently from nonpregnant CD patients. The authors concluded that cessation of smoking during conception may have played a role in the higher rates of relapse seen in UC compared with CD, but they could not explain why UC relapses were more common during first and second trimesters and postpartum, and not during the third trimester.[27] The time of peak AFP concentrations during pregnancy (around week 32) corresponds to the third trimester, when disease activity tends to be lowest.[28] During pregnancy, AFP levels start to rise at week 14, and during the first trimester they range from 18 to 119 ng/mL. The levels increase to 96–302 ng/mL during the second trimester, peak at 160–550 ng/mL during the third trimester, and then sharply decline postpartum.[29]

ANIMAL STUDIES OF AFP IN IMMUNE-MEDIATED INFLAMMATORY DISEASES

Evron and colleagues studied pregnant rabbits with experimental autoimmune encephalomyelitis (EAE; a T-cell-mediated model for multiple sclerosis) to determine whether pregnancy downregulates the immune response.[30] Both pregnant and nonpregnant rabbits were immunized with encephalitogenic material. All the nonpregnant rabbits developed EAE 3 weeks after immunization and died within 1–2 weeks.[30] In contrast, approximately 80% of rabbits that were immunized either before pregnancy or during the first half of pregnancy developed EAE, but mortality was reduced by 50% in animals immunized during the second half of pregnancy. Although the investigators concluded that pregnant rabbits had a less severe form of EAE and a longer duration of disease than nonpregnant rabbits, a mechanism was not determined and cell-mediated immune responses were not tested.[30]

To assess whether AFP expression was associated with the impact of protection against EAE in the second half of pregnancy, Irony-Tur-Sinai et al. induced 8-week-old mice with EAE and then treated them with a recombinant form of hAFP expressed in milk from transgenic goats. Administration of recombinant human AFP (rhAFP) was associated with decreases in central nervous system (CNS) inflammation and axonal degeneration and accompanied by significant improvements in symptoms and enhanced remission.[31] They also demonstrated that AFP was able to induce apoptosis of CNS T-effector cells, possibly allowing T-regulatory cells to exert unrestricted suppressive effects.[31]

Ogata et al. then modified transgenic mice to express human AFP and observed host defenses against both *Listeria monocytogenes* and induction of methylated bovine serum albumin–induced experimental arthritis, a model of RA. Mice expressing human AFP had a reduced production of cytokines after infection with *Listeria monocytogenes* and little to no histological evidence of arthritis (ie, synovitis, mononuclear cell infiltration, hyperplasia of the synovium, erosion of cartilage) compared with nontransgenic mice. They concluded that AFP markedly ameliorated the inflammatory consequences of experimental rheumatoid arthritis.[32]

Following the findings in RA, Matsuura and colleagues assessed whether AFP modulates disease severity of experimental autoimmune thyroiditis in mice, a model for Hashimoto's thyroiditis.[33] None of the mice expressing AFP developed thyroiditis. In contrast, monocellular infiltration was found in the thyroid tissue of 6 out of 8 control mice.[33] They also found a dose-dependent response to AFP on total numbers of thymocytes and CD4+ thymocytes in transgenic mice compared with controls. These findings led them to conclude that AFP not only downregulates thyroid peroxidase (TPO)–induced experimental autoimmune thyroiditis but may also play a role in altering T-cell development and T-cell-dependent autoimmune responses.[33]

More recently, investigators assessed rhAFP in animal models of acute colonic injury. Desreumaux et al. studied the efficacy of rhAFP compared with both placebo and anti-TNF-alpha in a mouse model of 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis. In this mouse model of acute colonic injury, rhAFP significantly reduced inflammation, decreased the level of myeloperoxidase, and downregulated pro-inflammatory cytokines, compared with both placebo- and anti-TNF-alpha-treated animals.[34] It remains to be determined how AFP may function in other animal models of IBD.

These animal studies provide a basis for evaluating AFP, not just as a marker of inflammation and regeneration, but as a potential therapy in chronic immune-mediated inflammatory conditions. However, to gain further understanding of how the modulation of disease activity by AFP could be clinically beneficial, several studies have attempted to further assess how AFP might modulate the disease activity of

chronic immune-mediated inflammatory conditions in humans (Table 2).

THE HUMAN CONNECTION BETWEEN IMMUNE-MEDIATED INFLAMMATORY DISEASES AND AFP

In 1974, Thompson et al. attempted to document a correlation between serum levels of AFP and the *activity* of inflammatory diseases in humans by monitoring serum levels of CEA and AFP in nonpregnant patients suffering from ulcerative colitis or Crohn's disease. Blood samples were obtained from patients during acute exacerbations (defined by clinical *symptoms*), periods of remission, and during intervals of low-grade (clinical) activity. Although the investigators did not find an association between blood levels of AFP and disease activity, defined by the terms "clinical remission" and "clinical exacerbation," there were several limitations to the study. The levels of AFP were much lower at baseline (21–86 ng/mL) than during pregnancy (300–600 ng/mL), and the definition of disease activity used was not substantiated by biologic activity (eg, C-reactive protein [CRP] or fecal calprotectin) or endoscopic mucosal evaluation.[35] Subsequently, studies have begun to evaluate disease activity in inflammatory conditions during pregnancy and in models that mimic the markedly elevated AFP levels seen in pregnancy.

Recognizing that women with myasthenia gravis (MG) experience remission during the second and third trimesters of pregnancy, Brenner and colleagues set out to determine whether correlations exist between MG activity and levels of AFP. They found that only amniotic fluid containing AFP significantly inhibited binding of myasthenia gravis antibodies to acetylcholine receptors, whereas amniotic fluid incubated with anti-AFP lost 60% of the inhibitory effect.[36] In addition, the inhibitory effect was dose dependent and increased when amniotic fluid was taken from pregnant women during their third trimester as compared with the second trimester. Elevated levels of AFP were able to downregulate the immune response of MG, suggesting that AFP levels contribute to remissions during the second and third trimesters of pregnancy and that low levels of AFP correlate with relapses seen during the postpartum period.[36]

Similarly, women with MS often have clinical remissions during the second and third trimesters of pregnancy. A retrospective study with 515 pregnant women suffering from MS assessed the timing and frequency of disease exacerbations and relapses during various time points of pregnancy. They found that there was significant reduction in relapse rates during the third trimester and a significant increase in postpartum relapses.[37]

MOVING FORWARD

Based on these immunoregulatory effects observed during pregnancy, Russian investigators evaluated hAFP as a therapy for IBD in a placebo-controlled clinical trial that enrolled 78 patients with either ulcerative colitis or Crohn's disease. After 30 days of treatment, 100% of the patients treated with hAFP had symptom improvement, 47% of patients had gained weight, and normal bowel movements were restored in 32% of the colitis and 30% of the Crohn's patients. In addition, the number of ulcerated lesions on endoscopy was reduced in subjects treated with hAFP, and almost 50% of hAFP-treated

TABLE 2. Animal Studies of AFP in Immune-Mediated Inflammatory Diseases

Authors	Disease	Animal Model	Conclusions
Evron S, Brenner T, Abramsky O (1984)[30]	Multiple sclerosis	Pregnant rabbits immunized with EAE, a model for multiple sclerosis	• Pregnant rabbits had a much less severe form of EAE and survived longer than nonpregnant rabbits•The pregnant rabbits that were best able to tolerate immunization with EAE were immunized later in pregnancy, when AFP levels are at their peak
Irony-Tur-Sinai M, Grigoriadis N, Tsiantoulas D, et al. (2009)[31]	Multiple sclerosis	Mice injected with mycobacterium tuberculosis and pertussis toxin	• Administration of AFP in mice with EAE was associated with decreases in CNS inflammation and axonal degeneration, symptom improvement, and enhanced remission
Ogata A, Yamashita T, Koyama Y, et al. (1995)[32]	Rheumatoid arthritis	Mice immunized with methylated bovine serum albumin into the knee joint	• Mice expressing human AFP had a reduction in the production of cytokines after infection with *Listeria monocytogenes*•AFP also ameliorates the inflammatory consequences of experimental rheumatoid arthritis in a mouse model
Matsuura E, Kang Y, Kitakawa H, et al. (1999)[33]	Autoimmune thyroiditis	Mice immunized with porcine TPO	• AFP downregulates TPO-induced experimental autoimmune thyroiditis•AFP may play a role in altering T-cell development and T-cell-dependent autoimmune responses
Desreumaux P, Rousseaux C, Rubuquoy C, et al. (2017)[34]	Colonic injury	Mice were infused with TNBS	• Recombinant human AFP injected into mice with TNBS-induced colitis significantly reduced inflammation, decreased the level of myeloperoxidase, and downregulated the pro-inflammatory cytokines compared with placebo- and TNFa-treated mice • The use of AFP was devoid of any toxic side effects

patients were able to stop using steroids. None of these findings or symptom improvements were observed in the placebo group.[38] Although this was the first study to evaluate parenteral administration of hAFP in patients with inflammatory bowel disease, the study had additional limitations to unconfirmed endoscopic or biomarker changes, including a small sample size and short study duration. This 30-day treatment period was insufficient to evaluate potential long-term adverse effects, including potential oncogenic properties of AFP.

Subsequently, in a randomized, double-blinded, placebo-controlled trial, rhAFP produced from milk of transgenic goats ("MM-093") was injected subcutaneously into patients with RA.[39] The pilot study targeted concentrations of AFP seen during the third trimester of pregnancy (300–500 ng/mL). Compared with patients receiving placebo injections, patients treated with MM-093 had significant improvements in their disease activity, as defined by patient's global assessment, pain, tender joints, swollen joints, CRP and erythrocyte sedimentation rate levels, early morning stiffness, and physician's global assessment.[39] The only reported adverse effects seen with the injections of AFP were headaches and injection site reactions (Table 3).[39]

CONCLUSIONS AND FUTURE DIRECTIONS

The experimental and clinical observations regarding AFP during pregnancy, and the association with timing of flares and quiescence of immune-mediated inflammatory diseases, provide clues to potential immunoregulatory roles. It makes teleological sense that an endogenous mediator would be able to prevent mothers from "rejecting" the fetus and vice versa. Evolving evidence suggests that AFP plays a role in immunoregulation by inducing T-cell suppressor activity,[8] downregulating dendritic-like cell antigen expression,[9] and impairing the function of macrophages.[10] Studies evaluating AFP and its effects in rodent models of autoimmune diseases have shown that AFP is associated with the downregulation of inflammation, including mouse models of IBD.

It has been long established that patients in remission before conceiving are more likely to maintain remission during pregnancy.[40] Conversely, patients with active disease before conceiving are more likely to have active disease throughout pregnancy.[40] Why exactly patients often have a more quiescent course during pregnancy is not known, but theories have suggested that the interplay between the maternal and fetal immune systems and the intestinal environment may be influenced by the immune tolerance needed to overcome the maternal and fetal HLA class II antigen disparity.[26]

Understanding the correlation between AFP and clinical disease activity during pregnancy in IBD and other immune-mediated inflammatory diseases may allow further insights into its role as an endogenous immunomodulator and, ultimately, as a potential therapy to modulate disease activity. Furthermore, the risks of AFP need better characterization, including potential oncological properties. Although no studies have shown that endogenous AFP stimulates novel oncogenesis, AFP receptors exist on the membranes of various tumor cells and play a large role in tumor proliferation by stimulating genes related to tumor growth. A study assessing AFP's role in tumor proliferation found that it upregulated certain oncogenes required for the growth of hepatocellular carcinoma.[41]

Nevertheless, these studies justify further evaluation of the role of AFP as an endogenous mediator of inflammation and as a potential therapeutic agent in immune-mediated inflammatory diseases. We propose further evaluation of AFP during pregnancy in IBD patients as a first step to better understanding the correlation of AFP and disease activity according to symptoms (patient-reported outcomes) and biomarkers

TABLE 3. Clinical Studies of AFP and Immune-Mediated Inflammatory Diseases

Authors	Disease	Disease Model	Conclusions
Brenner T, Beyth Y, Abramsky O (1980)[36]	Myasthenia gravis	Human gastrocnemius muscles obtained at biopsy and treated with sera from patients with myasthenia gravis	• AFP significantly inhibited the binding of myasthenia gravis antibodies to acetylcholine receptors in a dose-dependent manner
Abramsky O (1994)[37]	Multiple sclerosis	Retrospective study with pregnant women suffering from MS	• There was a significant reduction in relapse rates during the third trimester and an increase in relapse rates postpartum in women with multiple sclerosis•Pregnancy has a suppressive effect on disease activity of multiple sclerosis
Chereshnev V, Rodionov SY, Cherkasov VA, et al. (2004)[38]	Ulcerative colitis and Crohn's disease	Patients with either ulcerative colitis or Crohn's disease were injected with hAFP	• Clinical improvement without toxic side effects in those treated with hAFP compared with placeb•Decreased ulcerative lesions on endoscopy in those treated with hAFP compared with placebo
Pollard LC, Murray J, Moody M, et al. (2007)[39]	Rheumatoid arthritis	Patients with rheumatoid arthritis were injected with recombinant AFP	• Significant improvements in symptoms and disease activity in those injected with recombinant AFP compared with placebo

(fecal calprotectin) throughout pregnancy and postpartum. To differentiate between symptoms common in pregnancy (uterine cramping, constipation, vaginal bleeding), it will be necessary to go beyond symptoms and assess biomarkers (eg, calprotectin, CRP) as a surrogate for endoscopy. By studying how AFP levels during pregnancy correlate with disease activity, we can better anticipate and consider the potential use of an endogenously produced immunoregulatory therapy.

While exact physiologic roles for AFP remain elusive, it should be clear that AFP has more than the limited potential as a tumor marker and for the monitoring of fetal growth. These studies justify further exploration of the role of AFP as an endogenous mediator of autoimmune disorders and as a potential and novel therapeutic agent.

REFERENCES

1. Sell S, Skelly H. Tissue sites of alpha fetoprotein synthesis by the rat during pregnancy and hepatoma growth. *J Natl Cancer Inst.* 1976;56:645–648.
2. Thomas T. Structure and function of alpha fetoprotein. *Annu Rev Med.* 1977;28:453–465.
3. Mizewjewski GJ. *Alpha-Fetoprtein (AFP) and Inflammation: Is AFP an Acute and/or Chronic Phase Reactant?* New York: Department of Health, Division of Translational Medicine; 2015.
4. Kuo MT, Iyer B, Wu JR, et al. Methylation of the alpha-fetoprotein gene in productive and nonproductive rat hepatocellular carcinomas. *Cancer Res.* 1984;44:1642–1647.
5. Abu El Makarem M. An overview of biomarkers for the diagnosis of hepatocellular carcinoma. *Hepat Mon.* 2012;12:e6122.
6. Tancrede S, Bujold E, Giguere Y, et al. Mid-trimester and maternal serum AFP and hCG as markers of preterm and term adverse pregnancy outcomes. *J Obstet Gynaecol Can.* 2015;37(2):111–116.
7. Abelev GI, Perova SD, Khramkova NI, et al. Production of embryonal alpha-globulin by transplantable mouse hepatomas. *Transplantation.* 1963;1:174–180.
8. Murgita RA, Tomasi TB Jr. Suppression of the immune response by alpha-fetoprotein on the primary and secondary antibody response. *J Exp Med.* 1975;141:269–286.
9. Crainie M, Semeluk A, Lee KC, et al. Regulation of constitutive and lymphokine-induced ia expression by murine alpha-fetoprotein. *Cell Immunol.* 1989;118:41–52.
10. Atemezem A, Mbemba E, Marfaing R, et al. Human alpha-fetoprotein binds to primary macrophages. *Biochem Biophys Res Commun.* 2002;296:507–514.
11. Czokało M, Wiśniewski L. Inhibition of blastic transformation and immunoglobulin release in lymphocytes cultured in the presence of alpha-fetoprotein (AFP). *Exp Pathol (Jena).* 1979;17:176–180.
12. Wang W, Alpert E. Downregulation of phorbol 12-myristate 13-acetate-induced tumor necrosis factor-alpha and interleukin-1 beta production and gene expression in human monocytic cells by human alpha-fetoprotein. *Hepatology.* 1995;22:921–928.
13. Semeniuk DJ, Boismenu R, Tam J, et al. Evidence that immunosuppression is an intrinsic property of the alpha-fetoprotein molecule. *Adv Exp Med Biol.* 1995;383:255–269.
14. Dudich E, Semenkova L, Dudich I, et al. Alpha-fetoprotein causes apoptosis in tumor cells via a pathway independent of CD95, TNFR1 and TNFR2 through activation of caspase-3-like proteases. *Eur J Biochem.* 1999;266:750–761.
15. Um SH, Mulhall C, Alisa A, et al. Alpha-fetoprotein impairs APC function and induces their apoptosis. *J Immunol.* 2004;173:1772–1778.
16. Alisa A, Boswell S, Pathan AA, et al. Human CD4(+) T cells recognize an epitope within alpha-fetoprotein sequence and develop into TGF-beta-producing CD4(+) T cells. *J Immunol.* 2008;180:5109–5117.
17. Yang X, Zhang Y, Zhang L, et al. Silencing alpha-fetoprotein expression induces growth arrest and apoptosis in human hepatocellular cancer cell. *Cancer Lett.* 2008;271:281–293.
18. Yamamoto M, Tatsumi T, Miyagi T, et al. A-fetoprotein impairs activation of natural killer cells by inhibiting the function of dendritic cells. *Clin Exp Immunol.* 2011;165:211–219.
19. Yang X, Chen L, Liang Y, et al. Knockdown of alpha-fetoprotein expression inhibits hepg2 cell growth and induces apoptosis. *J Cancer Res Ther.* 2018;14:S634–S643.
20. Burow GN, Ferris TF. *Medical Complications During Pregnancy*. Philadelphia, PA: Saunders WB Publishing; 1975.
21. Abramsky O, Brenner T. Alpha-fetoprotein inhibits antibody binding to acetylcholine receptor. Significance for myasthenia gravis and other autoimmune diseases. *Isr J Med Sci.* 1979;15:943–945.
22. Götestam Skorpen C, Lydersen S, Gilboe IM, et al. Disease activity during pregnancy and the first year postpartum in women with systemic lupus erythematosus. *Arthritis Care Res (Hoboken).* 2017;69:1201–1208.
23. Nelson JL, Hughes KA, Smith AG, et al. Maternal-fetal disparity in HLA class II alloantigens and the pregnancy-induced amelioration of rheumatoid arthritis. *N Engl J Med.* 1993;329:466–471.
24. Confavreux C, Hutchinson M, Hours MM, et al. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. *N Engl J Med.* 1998;339:285–291.
25. Artlett CM, Smith JB, Jimenez SA. Identification of fetal DNA and cells in skin lesions from women with systemic sclerosis. *N Engl J Med.* 1998;338:1186–1191.
26. Kane S, Kisiel J, Shih L, et al. HLA disparity determines disease activity through pregnancy in women with inflammatory bowel disease. *Am J Gastroenterol.* 2004;99:1523–1526.
27. Pedersen N, Bortoli A, Duricova D, et al; European Crohn-Colitis Organisation-ECCO-Study Group of Epidemiology Committee-EpiCom. The course of inflammatory bowel disease during pregnancy and postpartum: a prospective European ECCO-EpiCom study of 209 pregnant women. *Aliment Pharmacol Ther.* 2013;38:501–512.
28. Adigun O, Bhimji S. *Alpha Fetoprotein (AFP, Maternal Serum Alpha Fetoprotein, MSAFP)*. Treasure Island, FL: Stat Pearls Publishing LLC; 2018.
29. Nielsen OH, Andreasson B, Bondesen S, et al. Pregnancy in ulcerative colitis. *Scand J Gastroenterol.* 1983;18:735–742.
30. Evron S, Brenner T, Abramsky O. Suppressive effect of pregnancy on the development of experimental allergic encephalomyelitis in rabbits. *Am J Reprod Immunol.* 1984;5:109–113.
31. Irony-Tur-Sinai M, Grigoriadis N, Tsiantoulas D, et al. Immunomodulation of EAE by alpha-fetoprotein involves elevation of immune cell apoptosis markers and the transcription factor FoxP3. *J Neurol Sci.* 2009;279:80–87.
32. Ogata A, Yamashita T, Koyama Y, et al. Suppression of experimental antigen-induced arthritis in transgenic mice producing human alpha-fetoprotein. *Biochem Biophys Res Commun.* 1995;213:362–366.
33. Matsuura E, Kang Y, Kitakawa H, et al. Modulation of T cell function by alpha-fetoprotein: an in vivo study on porcine thyroid peroxidase-induced experimental autoimmune thyroiditis in transgenic mice producing human alpha-fetoprotein. *Tumour Biol.* 1999;20:162–171.
34. Desreumaux P, Rousseaux C, Dubuquoy C, et al. P1280 - Anti-inflammatory effect of recombinant human alpha-fetoprotein (rhAFP) in the model of TNBS-induced colitis. Paper presented at: World Congress of Gastroenterology at ACG2017 Meeting; October 16, 2017; Orlando, FL.
35. Thompson WG, Gillies RR, Silver HK, et al. Carcinoembryonic antigen and alpha 1-fetoprotein in ulcerative colitis and regional enteritis. *Can Med Assoc J.* 1974;110:775–777.
36. Brenner T, Beyth Y, Abramsky O. Inhibitory effect of alpha-fetoprotein on the binding of myasthenia gravis antibody to acetylcholine receptor. *Proc Natl Acad Sci U S A.* 1980;77:3635–3639.
37. Abramsky O. Pregnancy and multiple sclerosis. *Ann Neurol.* 1994;36(Suppl): S38–S41.
38. Chereshnev VA, Rodionov SY, Cherkasov VA, et al. *Alpha-Fetoprotein*. Ekaterinburg: Uro RAN Russian Academy of Sciences; 2004.
39. Pollard LC, Murray J, Moody M, et al. A randomised, double-blind, placebo-controlled trial of a recombinant version of human alpha-fetoprotein (MM-093) in patients with active rheumatoid arthritis. *Ann Rheum Dis.* 2007;66:687–689.
40. Mogadam M, Korelitz BI, Ahmed SW, et al. The course of inflammatory bowel disease during pregnancy and postpartum. *Am J Gastroenterol.* 1981;75:265–269.
41. Li MS, Li PF, Chen Q, et al. Alpha-fetoprotein stimulated the expression of some oncogenes in human hepatocellular carcinoma Bel 7402 cells. *World J Gastroenterol.* 2004;10:819–824.