

Alpha-Fetoprotein (AFP) and Inflammation: Is AFP an Acute and/or Chronic Phase Reactant?

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Rec date: Jan 19, 2015, Acc date: Feb 12, 2015, Pub date: Feb 25, 2015

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Abstract

Even though alpha-fetoprotein has long been implicated with inflammation during pregnancy and adult liver dysfunction, the literature lacks a review of such a relationship. Clarification of the role of alpha-fetoprotein in the inflammatory response is explored in the present report regarding AFP's participation as a positive and/or negative phase inflammatory reactant. Inflammation follows a complex succession of vascular changes involving alternations in blood and lymphatic vessels both at local intracellular sites and at the organ (liver) level. The inflammatory response may result in either an acute phase or develop into a chronic phase following injury or insult from foreign bodies, microbes, toxins, carcinogens, or autoimmune self-antigens. The site of inflammation attracts pleiomorphic cell infiltrates which secrete various chemical mediators such as cytokines, chemokines, interferons, histamines, and a host of others. It is herein demonstrated that alpha-fetoprotein can serve both as an acute and a chronic phase reactant depending on its stage of ontogeny. It was found that alpha-fetoprotein functions as a positive acute phase reactant in the embryo, fetus, and placenta during pregnancy. In contrast, alpha-fetoprotein proceeds to function as a negative acute phase protein in the postnatal and adult periods of life, especially following liver dysfunction and toxic insult. In chronic viral-induced inflammation of the liver, especially viral hepatitis, alpha-fetoprotein appears to serve as a positive phase inflammatory reactant.

Keywords: Alpha-fetoprotein (AFP); Inflammation; Cytokines; Acute phase protein; Pregnancy; Interleukins; Monocytes; Macrophages; Inflammatory response

Introduction

Human alpha-fetoprotein (HAFP) is a tumor-associated fetal glycoprotein containing 3-4% carbohydrate moieties and a molecular mass of 69,000 daltons [1,2]. During development, HAFP is expressed and synthesized sequentially by cells of the yolk sac, and fetal liver and gastrointestinal tract [3]. In adults, the HAFP gene is silenced by methylation processes and AFP reappears only in instances of hepatic damage/regeneration and in solid tumors such as hepatomas and germ cell cancers [4].

Only adult hepatic oval cells surrounding bile ducts and blood vessels secrete HAFP; in contrast, liver parenchymal cells secrete little if any of the fetal protein [5]. AFP is synthesized in early S1 phase of the cell cycle and is secreted prior to the M phase [6]. The production of HAFP is initiated at the level of gene transcription and is proportional to the amount of available mRNA. Secretion of AFP from the hepatic oval cells occurs soon after synthesis with only minimal storage in the liver.

The half-life of HAFP has been determined to be 3-4 days in neonatal and pediatric populations and to be 5-6 days or more in the serum of adult cancer patients [7,8]. Thereafter, circulating "aged" HAFP is cleared from the bloodstream by asialoglycoprotein cell surface receptors on hepatic Kupffer sinusoidal cells and proteolytically degraded in the liver [9].

Inflammation in the fetus or adult is a local response of vascular tissue to irritation and injury involving a complex succession of changes which stem primarily from alterations in blood and lymph vessel flow to and from injured tissue. The changes are largely vascular and include increased blood flow, vasodilation, increased capillary permeability, and enhancement of cell adhesion processes and cell infiltration.

Thus, inflammation is a protective action of the innate immune response to injury or destruction of tissues, which serves to destroy, dilute, or wall-off both the injurious agent and the injured tissue. The process is one by which the body defends itself against harmful foreign and autoimmune agents including pathogens, toxins, carcinogens, irritants, self-antigens, and necrotic cells [10].

The inflammatory process halts injury and sets the stage for tissue repair and healing. Although inflammation and infection are often correlated, they are separate events and the inflammation stage can occur without infection. The major signs of inflammation are pain, redness, swelling, heat, and loss of function and mobility [11]. Some examples of inflammatory cells and mediators of inflammation such as vasoactive amines, cytokines, and eicosanoids are listed in Table 1 [12].

In addition, chemokines and their receptors have a role in the recruitment and attraction of leukocytes to the site of inflammation [13].

Cell Types	Inflammatory Chemical Mediators		Pro-inflammatory Cytokines	Anti-inflammatory Cytokines
1. Neutrophils	1. Heparin	15. Arachadonic acid	IL-1 α , β	IL-1, β
2. Basophils	2. Histamine	16. Endopeptidases	IL-2	IL-4
3. Eosinophils	3. Cytokines	17. Fibrinopeptides	IL-3	IL-5
4. Mast Cells	4. Chemokines	18. Lysolipids	IL-6	IL-6
5. Macrophages	5. Serotonin	19. Platelet Activating Factor	IL-8	IL-7
6. Monocytes	6. Interferons	20. Phospholipase-2	IL-12	IL-10
7. Keratinocytes	7. Kinins	21. Cyclo-oxygenase	IL-15	IL-11
8. Endothelial Cells	8. Bradykinin	22. Nitric oxide-oxidase	IL-17	IL-13
9. Fibroblasts	9. Eicosanoids	23. G-Colony Stimulating factor	IL-18	IL-16
10. Regulatory T-cells (tregs)	10. ICAMs	24. GM-Colony Stimulating factor	IL-20	IL-35
11. Microglia	11. Prostaglandins	25. Neutral Proteases	IL-25	TGF- β
12. Mononuclear Cells	12. Leucotrienes	26. Interleukins	IL-33	IFN- α
13. Platelets	13. Nitric Oxide		TNF- α	G-CSF
14. Dendritic Cells	14. C3a, C5a		IFN- γ	IL-1RA

Table 1: Listings of inflammatory-associated cells, mediators, and cytokines are displayed. The cytokines are individually presented as pro-inflammatory and anti-inflammatory types. Please note that the table is to be read down the columns only, not across the rows. *Note IL-1 and IL-1 β can act both as Pro- and Anti-inflammatory cytokines depending on type of activation. C3a, C5a = Complement Factors – 3a and 5a; ICAMs = Intercellular Adhesion Molecules; G-colony = Granulocyte Colony; GM = Granulocyte/Macrophage; IL = Interleukins; TNF = Tumor Necrosis Factor; IFN = Interferon; TGF = Transforming Growth Factor. Data extracted from references [10,12,13,83].

The two types of inflammation are viewed as an acute and a chronic phase. The acute phase reactants are a class of proteins whose serum levels increase or decrease in response to inflammation. In response to acute tissue injury, local infiltrating inflammatory cells (granulocytes) secrete a number of cytokines including the interleukins (ILs), tumor necrosis factor-alpha (TNF- α), and related proteins (Table 1). The pro-inflammatory cytokines include the interleukins, interferons, tumor necrosis-associated factors and others (Table 1) [14]. In addition, the liver can respond by secreting a number of acute phase proteins; this event constitutes the positive acute phase response. Simultaneously, the production of a number of other liver derived proteins are down-regulated and their levels reduced; this represents the negative acute phase response.

The positive acute phase proteins (APPs) such as alpha-fetoprotein (AFP) can serve other functions such as participating in innate immune responses and in blood clotting activities. Some positive APPs aid in inhibiting the growth and spread of microbes; these include C-reactive protein, mannose-binding protein, ferritin and others listed in Table 2 [15]. Some APPs stimulate the coagulation process; these include the blood coagulation factors [15]. The trapping of pathogens in local blood clots can also serve to limit infection processes. Furthermore, the coagulation factors can function in the innate immune system by increasing vascular permeability to local inflammation areas and serve as chemotactic agents for phagocytic cells.

I. Acute Phase Inflammation		
Positive Phase Proteins	Negative Phase Proteins	Experimental Injury Reactants
Alpha-fetoprotein	Albumin	Turpentine
Mannose Receptor	Transferrin	Carbontetrachloride
Complement Fixation	Transthyretin	Galactosamine
Ferritin	Retinol-B Protein	Ethionine

Ceruloplasmin	Antithrombin	Croton Oil
Serum Amyloid-A	Transcortin	Polyacrylamide Beads
Haptoglobin	Alpha-2-macroglobulin	Thioacetamide
C-reactive Proteins	Alpha-albumin	Allyl Ethanol
II. Developmental Disorders Associated with Acute Inflammation Accompanied by Elevated Alpha-fetoprotein (AFP) in the Maternal/Placental/Fetal Axis. Parenthesis () denotes AFP Multiple of Median (MOM) derived from ng/ml.		
1. Preterm Delivery (3.3)	6. Chronic Villitis (4.7)	11. Epidermolysis bullosa (2.1)
2. Intra-uterine Growth Retardation (2.5)	7. Placental Abruption (2.6)	12. Gastroschisis (8.0)
3. Placenta Accreta (2.3)	8. Bronchopulmonary Dysplasia (2.8)	13. Premature Membrane Rupture (2.6)
4. Placental Vascular Lesions (2.5)	9. Placenta Previa (2.5)	14. Fetoplacental Ischemia (4.1)
5. Intervillous Thrombosis (2.6)	10. Chorioamnionitis (2.1)	15. Placental Mesenchymal Dysplasia (2.7)

Table 2: Lists of reactant proteins of the acute phase versus the chronic phase of inflammation are presented in Section I; while the experimental injury and virus toxin reactants are listed in Section II.* In Section III, the various disorders associated with acute inflammation in the fetal/placental unit during development are presented. See text for reference citations of the acute versus the chronic phase of inflammation. Group I data extracted from references [15,17,18]. Group II data extracted from references [48,78,84-97].

In contrast to the positive acute phase response, the negative acute phase response exhibits reduced APP levels (i.e. albumin) during the inflammation process. The down regulation of APPs is regulated by transforming growth factor- β in fetal and adult liver cells [16]. Examples of negative APPs encompass transferrin, transthyretin, and those included in Table 2 [17]. Still other APPs, such as Serpins (α -1-anti-trypsin), provide a negative feedback in the inflammatory response. The reduced serum levels of the negative APPs have also been employed as biomarkers of inflammation. In effect, decreasing the liver synthesis of such proteins could be viewed as a process to conserve amino acid reserves for producing positive APPs in an efficient fashion.

Objectives

A review pinpointing the relationship between alpha-fetoprotein (AFP) and inflammation is currently absent in the biomedical literature. Hence, the objectives of the present review are to determine whether AFP is: 1) associated with inflammation; 2) an acute or chronic phase reactant; 3) if acute, is AFP a positive or negative reactant and 4) if chronic, with what disorders is AFP associated?

Activation of nuclear proto-oncogenes

The acute inflammatory reaction represents a physiological event of important metabolic adjustments by the liver with dramatic changes in the pattern of expression of several liver-derived plasma protein genes, including the AFP gene [18]. Liver cell (parenchyma) replication in response to growth factors or partial hepatectomy is manifested by a series of cellular gene activations concurrent with cell cycle passage from G0 to G1 phase. This activation (without DNA synthesis) of a set of genes is referred to as an "immediate early gene response" which includes the nuclear proto-oncogenes c-fos, c-jun, c-myc, and the AFP gene. A later activation occurs in the p53 gene, cKRAS and d-HRAS genes [19]. AFP synthesis is normally repressed in adult liver cells, but

is re-activated in the early phases of hepatocyte regeneration following partial hepatectomy [20-22]. Also, following turpentine-induced acute inflammation in the rat, activation of the nuclear oncogenes (c-fos, c-jun, c-myc) together with 2 gene transcripts of the AFP gene are triggered after 4-12 hrs and after 4-24 hrs, respectively, following initiation of inflammation in the adult rat [23]. The accumulation of mRNA in all 4 genes was found to occur throughout all lobular zonal regions of the liver. An inhibition of DNA synthesis and mitosis is prolonged for 48 hrs after induction of the inflammatory response. Thus, acute inflammation induces the induction of several oncogenes and the AFP gene in rat hepatocytes, but activation of cell cycle G1 phase is not followed by mitosis and cell division.

Regarding cancer, it is being increasingly accepted that the chronic inflammatory process is inherently associated with various cancer types, especially human hepatocellular carcinoma (HCC). To this end, reports have shown that AFP can induce the expression of certain oncogenes in cell cultures of HCC. For example, it has been demonstrated that AFP could stimulate the mRNA expression of c-fos, c-jun, N-ras and mutated forms of p53 and p21 (ras) after 6-12 h incubation in HCC cell cultures [24]. Hence, AFP was found capable of promoting the expression of certain oncogenes to enhance cell growth and proliferation of human liver cancer cells.

It is of further interest that fatty acids have been reported to regulate AFP gene expression. In rats, treatment with arachidonic acid analogues specifically led to low mRNA AFP levels in cultured yolk sac explants [25]. As discussed in a later section below, AFP levels in certain fetal birth defects may be modulated by the maternal nutritional intake of omega-3 and omega-6 fatty acids which are substrates for the pro-inflammatory eicosanoids. In the yolk sac study, transfection experiments were also performed in HepG2 hepatoma cultured cells which showed that the AA analogues decreased the transcriptional activity of the 7 kb regulatory region of the AFP gene. The 330 bp AFP promoter was identified as the target for the AFP mRNA down-regulatory effect.

AFP, eicosanoids, and inflammation

Eicosanoids are inflammation-associated signaling molecules derived from either omega-3 or omega-6 fatty acids. Leukotrienes (LKT) are a family of eicosanoid inflammatory mediators synthesized in peripheral monocytes and other cells by the oxidation of Arachidonic (C20) fatty acid and obtained from T-cell secretions [26,27]. LKTs use lipid signaling to convey information in both an autocrine and paracrine fashion in order to regulate immune responses. LKT cell synthesis is usually accompanied by the inflammatory mediators histamine, thromboxane, and prostaglandins produced by monocytes and macrophages [28]. The overproduction of LKTs trigger smooth muscle contractions in bronchioles and blood vessels which are major events in inflammation resulting in airway and blood vessel constriction. The LKTs also have a chemotactic effect on neutrophils causing migration into tissue areas of intrusion, damage, and insult. AFP is able to specifically bind Arachidonic acid, the major precursor for LKT and prostaglandin synthesis [29]. In the latter study, AFP was found to reduce prostaglandin synthesis, the release of unmetabolized Arachidonic acid, and to enhance LKT production in monocytes. When indomethacin is combined with AFP in the treatment of lymphoma cells, prostaglandin is restored, a very high Arachidonic acid mobilization occurs, and the production of LKT and cyclooxygenase is enhanced [30,31]. Thus, AFP was shown to influence eicosanoid metabolic pathways in both monocytes and lymphoma cells which could partly explain some of the pro-inflammatory effects of AFP.

AFP and inflammation during pregnancy

When the normal progression of pregnancy is threatened, inflammatory processes are often amplified in order to minimize detrimental effects and eliminate noxious agents. AFP is a gestational-age-dependent, tumor-associated oncofetal 69KD protein which is associated with both fetal defects and malignant tumor growth [1]. During embryonic and fetal development, AFP is capable of modulating, restricting or regulating several different states of inflammation and unwanted growth during histogenesis and organogenesis [2]. Thus, AFP has been reported to serve as an acute phase protein of inflammation in both a positive and a negative manner depending on the development stage of ontogeny. For example, during pregnancy AFP has been shown to be a positive marker of acute inflammation, while in the postnatal and adult periods, AFP behaves as a negative acute phase reactant (see below). In second trimester pregnancy, elevated amniotic fluid AFP was reported to be associated with 59% of pregnant women that displayed elevated levels of Intracellular Adhesion Molecule-1 (ICAM-1), a known marker of acute inflammation. The combination of elevated AFP together with elevated ICAM-1 levels were correlated with pre-term birth, intrauterine growth retardation (IUGR), and prematurity [32]. AFP is known to bind to caspases; such agents are activated to mediate proteolytic processing of proinflammatory cytokine IL-1 β , levels of which are elevated in some forms of preterm birth and maternal metabolic disorders [33,34].

During human pregnancy, mid-trimester elevations of maternal serum (MS) AFP have identified various groups of patients with a 2- to 3-fold increased risk of intrauterine growth retardation (IUGR) [35]. In this instance, it was proposed that the elevated MSAFP was caused by a fetomaternal bleed from a chorionic decidual-placental separation (an inflammatory lesion) resulting in placental insufficiency and poor weight gain in third trimester pregnancy [35,36]. Investigators have

since found that some AFP elevations result from inflammatory placental pathologies at term, namely, 1) chronic villitis, 2) placental vascular lesions of infarction and 3) intervillous thrombosis [36] (Table 2). Women with chronic villitis also displayed elevated AFP levels together with low birth weight offspring, both conditions of which have a recognized association with IUGR. An inflammatory process may have permitted the transudation of fetal proteins into the maternal circulation, thereby causing the elevated mid-trimester MSAFP levels. Another group of clinical investigators reported that elevated second trimester AFP conveyed a significant risk of low birth weight and neonatal death; both exemplify features of AFP as a positive APP [37]. Furthermore, elevated AFP has been associated with the presence of maternal vascular uterine lesions that compromised the blood supply to the vascular bed of the placenta, leading to placental ischemia and chronic villous damage; these lesions resulted in an increased flow of AFP to leak into the maternal circulation [36,38,39]. Finally, premature rupture of membranes is an inflammatory event following intrauterine fluid leakage which can occur as early as 22 to 26 and as late as 36 weeks gestation [38]. MSAFP is elevated during this placental interface event which can further result from chorioamnionitis and local inflammation of fetal membranes.

A respiratory prenatal disorder associated with an inflammatory response during pregnancy is fetal Bronchopulmonary Dysplasia (BPD). This disorder occurs in premature infants who present with immature lungs at delivery and require assisted ventilation with high concentrations of inspired oxygen [40,41]. Both positive and negative inflammatory factors were found to be associated with BPD [42]. The amniotic fluids and cord bloods in newborns who had BPD showed elevated inflammatory markers and proinflammatory mediators such as chemokines, adhesion molecules, pro-inflammatory cytokines and proteases (Table 1). In contrast, less of the anti-inflammatory cytokines were present at the inflammatory sites. In maternal blood during the 2nd trimester, levels of MSAFP and MSHCG were both found to be elevated, while MS μ E3 levels were low in BPD-afflicted newborns.

In a further example of AFP modulated inflammation during pregnancy, the maternal nutritional intake of polyunsaturated fatty acids (PUFAs) may be involved [43]. Fetal AFP levels are increased in the presence of an abdominal ventral wall defect termed gastroschisis, which represents a disruption in intrauterine blood flow caused by a herniation of abdominal organs. Omega-6 PUFAs are substrates for eicosanoid and cytokine synthesis, are prone to oxidation, and play a role in modulating inflammation, immune function, and vasculogenesis. A higher maternal intake of palmitoleic and linoleic dermal fatty acids was found associated with an increased risk of gastroschisis [44]. The maternal risk involved fatty acid desaturation activities resulting in high level of palmitoleic acid, and low levels of oleic acid during pregnancy, and high level of docosahexanoic acid at delivery. It is of interest that AFP has been reported to affect the fatty acid desaturation of fatty acids such as linolenic acid [45]. The mechanism by which gastroschisis occurs, may be a combination of inflammatory processes and oxidative stress leading to a vascular disruption. Overall, these findings suggested that early maternal inflammatory processes resulting from an imbalance of fatty acids, could lead to vascular disruptions; this may be the underlying mechanism responsible for at least some of the cases of the gastroschisis defects during 3rd trimester pregnancy.

As a final example of AFP-associated inflammation, both maternal serum (MS) and amniotic fluid (AF) AFP levels are elevated in cases of Epidermolysis bullosa (ELB). ELB is a highly lethal, inherited, autosomal recessive disorder associated with thin, erosive, blistered fetal skin, dilated stomach, and pyloric atresia [46]. The amniotic fluid (AF) of such fetuses contained high levels of acetylcholinesterase (Ache) enzyme, however, the karyotype was normal. Some fetuses further displayed mutated integrin-alpha-6 and B4 genes, kidney malformations, hypoplastic or absent hemi-desmosomes along the dermal-epidermal junction, and aplasia cutis congenital [47,48]. Fetal skin biopsies are usually performed but can produce false positive results unless electron microscopic examination is available. The inflammatory lesions involve a unique abnormality of the placental membranes which show existence of two extra membraneous sacs [49]. Elevated MSAFP MOM values (derived from ng/ml) usually exceed 3.0 MOMs, while elevated AFAFP MOMs can attain values as high as 13.7 MOMs [50]. It has been suggested that prenatal determination of MSAFP, AFAFP, and AF-Ache may obviate the need for fetal skin sampling in the prenatal diagnosis of this disorder.

Acute inflammation induced by experimental injury

In pregnant mice, maternal serum AFP was found to increase two-fold following a single subcutaneous injection of turpentine into the dam [51]. Concurrently in the fetus, a 25% reduction in serum AFP levels was observed; this was in keeping with a 35 to 45% decrease in serum AFP reported within the first 21 days following birth [52]. In further experiments of the induction of experimental injury, adult rats were administered either croton oil, carbon tetrachloride (CCl4), galactosamine (GLTA), or ethionine (ETN) [53]. Elevations of serum AFP occurred after administration of the hepatotoxic agents (CCl4, GLTA) and the liver carcinogen ETN, but not after croton oil injection. While CCl4 induced AFP elevations to 345 ng/mL after 4.0 days, low doses of GLTA increased AFP levels to 12,700 ng/mL at 6.0 days. In ETN-treated rats, AFP levels attained 19,000 ng/mL by day 3.0 post injection. It was evident from these studies that AFP served as a positive acute phase reactant regarding the liver of rats exposed to hepatotoxins and carcinogens, but not to non-toxic croton oil. In further studies of animal inflammation, polyacrylamide beads were employed to induce granulomas housed in subcutaneous pouches in

the skin of adult mice; this resulted in renewed AFP syntheses in the liver [54]. The results of this study showed that circulating AFP was preferentially taken up by cells of the granuloma tissue which consisted of macrophages, mononuclear cells, and polymorphonuclear cells. In this induced granuloma bioassay, AFP behaved as a positive acute phase reactant. In a final study, skin cultures of human keratinocytes were incubated together with T-lymphocytes; addition of AFP to the cultures resulted in enhanced baseline expression of cytokines, chemokines, and growth factors [55]. These cytokine agents induced a positive inflammatory cellular response and AFP further induced tumor necrosis factor-alpha (TNF-α) to stimulate expression of monocytic chemotactic Protein Factor-1 and the chemokine IP-10. AFP also caused a marked increase in levels of Protein-1 activator in activated keratinocytes and increased levels of H₂O₂ and modulated nitrite/nitrate levels in non-cytokine stimulated keratinocytes. In summary, AFP is capable of modulating inflammatory activities in human skin cells in culture.

AFP and chronic inflammation

If the conditions causing acute inflammation are not resolved, the inflammation may transition into a longer time period termed the chronic phase. Chronic inflammation is a prolonged process resulting in tissue destruction, new connective tissue formation, fibrosis, necrosis, and cell infiltrations of monocytes, macrophages, lymphocytes (T- and B-cells), and dendritic cells. Unlike the acute inflammatory response, the virus-induced inflammatory response is involved only in chronic inflammation. After a viral infection, multiple proinflammatory mediators (i.e. chemokines and their receptors, Table 1) contribute to recruitment of immune cells to the liver and to the generation of an antiviral immune response [56]. Chronic inflammation is found in liver-related disorders such as neonatal hepatitis (NH), hepatitis-C virus (HCV), and hepatitis-B virus (HBV) often associated with hepatic cirrhosis. It is germane that AFP has been implicated in all forms of chronic hepatitis (Table 3). In neonatal infants of 2-14 weeks, 10 of 11 infants with NH displayed elevated levels of AFP exceeding 40,000 ng/ml [57]. In a further study of NH, 65% of patients exhibited elevated AFP levels in NH with the higher AFP levels correlating with the more severe inflammatory changes in the liver.

I. Chronic Phase Inflammation	II. Chronic Autoimmune Inflammation Disorders	III. Autoimmune Chemical Apoptosis Mediators
1. Chronic Hepatitis	1. Rheumatoid Arthritis	1. MHC Class-II Proteins
2. Alcoholic Cirrhosis	2. Multiple Sclerosis	2. CCR5 Chemokine Receptors
3. Virus-B Hepatitis	3. Myasthenia Gravis	3. TF-Fox P3
4. Virus C Hepatitis	4. Allergic Encephalomyelitis	4. BAX (bcl-2-like Protein 4)
5. Aflatoxin	5. Systemic Lupus Erythromatosus	5. BID (BH3 Interacting Domain)
6. N-2-Fluorenyl-acetamide	6. Induced Joint Arthritis	6. BAD (bcl-2 death Prompter)
7. N-hydroxy-N2-fluorenyl-acetamide	7. Hemolytic Anemia ABO Isoagglutination	7. FASL (CD95) Ligand
8. Hepatocellular Carcinoma	8. Complement-Dependent Oligodendrocyte Lysis (Galactocerebroside)	8. FASR (FAS Receptor)
9. HBx Protein (virus-B associated)	9. NZB Murine Lupus	9. TRAIL (Apoptosis Inducer)
10. Cholangiocarcinoma	10. Autoimmune Hepatitis	10. Caspases-3,8,10

11. Biliary Cirrhosis	11. Autoimmune Uveitis		11. Dysregulated p53		
12. Hemochromatosis	12. Psoriasis		12. AIF		
IV. Serum alpha-fetoprotein (AFP) concentrations (ng/ml) in patients with chronic liver disorders					
	Total	AFP < 40 ng/ml	AFP > 40 ng/ml	AFP Range	AFP Median
Name of Disorder	# Patients	# Patients	# Patients	(ng/ml)	(ng/ml)
1. Hepatic Cirrhosis	20	11	9	50-900	490
2. Chronic Hepatitis	92	69	23	40-480	100
3. Viral Hepatitis	176	109	67	45-3000	210
4. Drug Hepatitis	18	13	5	40-475	190
5. Alcoholic Hepatitis	40	34	6	50-490	90
6. Non-Hepatic Disorders (Controls)	350	350	0	20-May	8

Table 3: Lists of chronic phase reactants and autoimmune inflammation disorders are presented in sections I and II. The inflammatory mediators of chronic autoimmune disorders are shown in Section III. # = number; FAS = first apoptosis signal; FASL = FAS ligand; AIF = apoptosis-inducing factor; TRAIL = TNF-related apoptosis-inducing ligand. Data extracted in Group I from references [86-88,90,92]; Group II from references [57-60,89].

In one study of hepatitis-C virus-induced inflammation, 24% of infected patients demonstrated elevated AFP levels [58]. This report revealed that elevated AFP levels were associated with age, fibrosis, histologically observed inflammation, abnormal liver enzymes, and total bilirubin levels. A second study involving HCV also showed that elevated AFP concentrations correlated with low platelet counts, reduced albumin levels, decreased liver enzymes, fibrosis, and insulin resistance [59]. In comparison to the above, HBV infected patients also displayed elevated AFP levels (2,000 ng/mL), while AFP levels in patients of HBV combined with liver cancer showed AFP increases of 10-fold (20,000 ng/mL) [60]. Finally, in HBV-infected patients, elevated AFP levels were again higher in patients that also had liver cancer than in patients with only HBV [60]. Overall, it becomes clear that AFP serves as a positive chronic inflammatory agent in virus infections (Table 3).

Dietary inflammatory agents

The rise of serum AFP due to liver inflammation can also be caused by dietary hepatoxins. Aflatoxin B1 is a naturally-occurring mycotoxin produced by the fungus, *Aspergillus flavus* which is a highly carcinogenic liver toxin [61]. The fungal mold is most noted for contaminating vegetables and grains prior to harvest and during storage. In countries with high incidences of hepatocellular carcinoma (HCC), diet-derived AFB1 has been detected in 55% of HCC patients displaying elevated serum AFP levels [62]. Ingestion of moldy foods containing AFB1 can cause serum AFP elevations due to the initial induction of liver inflammation and subsequent carcinogenesis [63-66]. Moreover, AFP has been shown to bind AFB1 with an affinity association constant of 3.7×10^{-5} M at the same hydrophobic dye-binding site on AFP that binds aniline-naphthalene-sulfonate [67]. An earlier study had demonstrated that AFP serum elevations by AFB1 were comparable to those produced by chemical carcinogens such as diethylnitrosamine, N-2 fluorenylacetamide, and N-Hydroxy-N2-fluorenylacetamide [68, 69]. In 1994, a study of dietary intake of AFB1 in 35% of patients from the country of Ghana showed the presence of

the mycotoxin or its metabolites in their blood circulation following instances of liver inflammation; all patients tested had elevated serum AFP levels [70].

AFP and autoimmune neuroinflammation

Alpha-fetoprotein (AFP) has long been implicated with autoimmune disorders including those of the central nervous system (CNS). AFP was found to be associated with myasthenia gravis (MG) and played a protective role against autoimmunity during pregnancy. Studies pioneered by Abramsky and Brenner [71] demonstrated that AFP was one of the major factors produced during pregnancy that immunosuppressed MG by inhibition of autoantibody to the acetylcholine receptor [72]. Subsequently, AFP in pregnancy was demonstrated to suppress immune allergic encephalomyelitis EAE (an animal form of multiple sclerosis) by lowering the level of antibodies produced against myelin basic protein in EAE and amelioration of disease immune reactions [73]. AFP was further elevated in pregnant NZB mice displaying system lupus nephrotic symptoms as compared to disease-free pregnant mice [74]. AFP can also produce remissions in multiple sclerosis (MS) patients during human pregnancy [72]. Using recombinant human AFP (RHAFP) in animal models of EAE, RHAFP markedly improved the clinical manifestation of EAE by preventing CNS inflammation and axonal degeneration [75]. In a prior study, T-cells from AFP-treated mice significantly reduced activity toward myelin oligodendrocyte glycoprotein (MOG), a MS mediator and antigen, and exhibited less T-cell proliferation and reduced TH1 cytokine secretion. In addition, AFP affected the humoral immune response and caused an inhibition in MOG-specific antibody production. The expression of DB11 to MHC Class II protein and chemokine receptor CCR5 was also down regulated in monocytes and macrophages. In all these studies, AFP was well-tolerated and served to decrease various aspects of neuroinflammation, including disease severity, axonal loss and damage, and T-cell reactivity and antigen presentation [76]. In subsequent experiments by these 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 further found to increase the expression of the pro-apoptotic factors BaX, Bid, and others in peripheral lymphocytes (Table 3). 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 [76,77]. A further 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 bloodstream [78]. AFP was found instrumental in suppression of the induced autoimmune arthritis in the mouse model and functioned as an immunosuppressant agent to ameliorate the development of this inflammatory autoimmune disease. Serum AFP levels were 500 times higher in the transgenic mice than in the blood of control mice. Other chronic autoimmune inflammatory disorders associated with AFP biological activities are displayed in Table 3.

As mentioned above in inflammation during pregnancy, AFP has been reported to interact and bind to caspase-3,9 enzymes (cysteine proteases) which constitute key components of molecular complexes called inflammasomes [34,79]. These inflammation-induced organelles are multiprotein oligomer formations that enhance inflammatory processes leading to cell death [80]. Inflammasomes are assembled through interactions among death domain superfamily members especially the CARD (caspase activation and recruitment domain) and pyrin (PYD) domains [81]. These domains can polymerize to form filaments using domain-to-domain interfaces to recognize autoimmune, infectious, and stress induced inflammatory events. The inflammasome molecular platform triggers the maturation of the proinflammatory cytokine interleukin-1 β to engage innate immune defense processes [82]. A strong association exists between dysregulated inflammasome activity and human heritable and acquired inflammatory diseases. One such disease is autoimmune gout due to elevated blood uric acid levels and characterized by severe joint inflammation resulting in arthropathy and considerable pain [80]. Other inflammasome-involved diseases include cold inflammatory syndrome, Muckle-Wells syndrome, Beckwith-Wiedemann syndrome, and Type-II diabetes.

Conclusion

Prior to this report, the relationship between AFP and inflammation had not been fully clarified and elucidated in the literature. It is apparent from the above discourse that AFP is indeed an inflammatory reactant serving both as a positive and a negative acute response agent. The positive or negative response appears dependent on the ontogenetic stage at which AFP is being expressed. During acute inflammation in pregnancy, AFP levels are increased in conditions such as pre-term birth, intra-uterine growth retardation, prematurity, fetal-maternal bleed, premature membrane rupture; also included are placental inflammatory events such as chronic villitis, ischemia, intervillitis thrombosis, and chorioamnionitis. From such reports, it is apparent that AFP can serve as a delivery biomarker at term pregnancy. Such lesions can result in placental insufficiency and poor weight gain during late pregnancy. AFP was also found elevated in acute experimental injury and in chronic virus-induced inflammation of the liver due to chemical and dietary hepatotoxins. AFP also serves as negative phase reactant in the postnatal period exemplified in experimental turpentine injections, clinically as neonatal death, and in adult liver dysfunction. Thus, the role of AFP as an indicator or biomarker of inflammation has yet to be better

understood and utilized in clinical practice during pregnancy and adult liver disorders.

Acknowledgment

The author wishes to thank Ms. Tracy Godfrey for the typing, processing, and organization of this manuscript for publication.

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