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Are Alpha-Fetoprotein Based-Vaccines Potential Tools for Liver Cancer Therapy?

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Alpha-Fetoprotein (AFP) is a tumor-associated oncofetal antigen consisting of a single polypeptide chain with a molecular mass of 69 kDa and a carbohydrate content of 3-5% [1]. AFP is produced in the fetal yolk sac at 9 weeks of gestation, and later in the fetal liver and gastrointestinal tract [1]. AFP binds and transports a multitude of ligands and is re-expressed in adult life in several tumors including hepatomas, hepatoblastomas, pancreatic, stomach, yolk sac tumors, and teratomas [2]. Accordingly, serum AFP has been employed as a biomarker to monitor cancer recurrence after treatment and to reveal pregnancy and neonatal disorders [2]. However, the specificity and sensitivity of serum AFP values change according to the cut-off value employed in Hepatocellular Carcinomas (HCC) [2].

Recently, it has been demonstrated that AFP can exert immunomodulatory and immunosuppressive activities *in vitro*. Indeed, Natural Killers (NKs), activated lymphocytes, Cytotoxic T Lymphocytes (CTLs) and Antigen Presenting Cells (APCs) can be immunosuppressed by AFP [3-5]. On the other hand, humoral and T cell immune responses to AFP have been detected in patients affected by HCC or other liver diseases including cirrhosis [6,7]. High titers of anti-AFP antibodies in HCC (14/60), liver cirrhosis (3/15) and chronic hepatitis (1/15) patients but not in 40 healthy individuals were detected [6]. Butterfield et al. demonstrated for the first time that human T-cells can recognize AFP epitopes in the context of HLA-A2.1 [7]. In addition, AFP peptide-specific T cells were able to recognize AFP-transfected cells [8]. Based on these studies, different AFP peptides were identified as "immunodominant" according to their strong binding to MHC I, *in vitro* high-level production of IFN-γ and activation of CTLs from stimulated healthy donor T cells [7,8]. These evidences have supported the design of AFP-based cancer vaccines, although AFP is a self antigen. Indeed, different studies have reported that tolerance to AFP could be interrupted [6-8]. Different approaches of immunization, including the delivery of AFP (alone or with cytokines) by DNA, Dendritic Cells (DCs), viral vectors or as a recombinant protein as well as different experimental models have been used to evaluate whether AFP immunization could induce a protective immunity in HCC bearing animals [9-12]. Vaccination with DCs carrying AFP epitopes or AFP-plasmid DNA has been demonstrated to inhibit the growth of transplanted syngeneic AFP-positive hepatoma cell lines without inducing autoimmune reactions against the regenerating liver [11,12]. Overall, AFP-based cancer vaccines have shown encouraging results in preclinical studies. In agreement with these preclinical results, clinical trials were carried out in patients with HCC [13,14]. Butterfield et al. performed two trials in heavily pre-treated HCC patients using AFP-derived peptides delivered in adjuvant or carried by DCs. The authors demonstrated that patients generated T-cell responses to most or all of the peptides without evidence of toxicity. However, these trials did not achieve significant objective clinical responses [13,14]. Other human studies were conducted to find modalities to implement immune responses to AFP for future clinical trials.

Major concerns for the use of AFP as an anti-cancer vaccine rely on the fact that AFP is a self antigen, exerts an immunosuppressive activity, inhibits apoptosis of cancer cells and stimulates the expression of some oncogenes [1,3-5,9]. On the other hand, no adverse reactions due to autoimmune phenomena have been observed in preclinical and clinical trials and AFP immunization was shown to induce a strong immune response both in immunized animals and humans [9,11-14]. In addition, both native AFP and a recombinant AFP fragment of about 300 amino acids composed of the last half of the full-length AFP molecule were demonstrated to inhibit the growth of estrogen-dependent breast cancer cells transplanted in mice [15,16].

Overall, although preclinical studies employing AFP-based vaccines were satisfactory, results in HCC patients were not encouraging. Accordingly, further studies are necessary to better elucidate the effects of AFP-based cancer vaccines on the innate and adaptive immunity, to develop new vaccine scheduling and to improve the use of the vaccine in clinical trials. It will be necessary to envisage new clinical trials combining AFP-based cancer vaccines with conventional therapies to better prevent and treat AFP-expressing tumors in patients.

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