LETTER

Immunomodulation by alpha-fetoprotein in neurological disorders may involve oncogenic dilemmas

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Dear Editor:

Recent data provide new roles for alpha-fetoprotein (AFP) in controlling the autoimmune inflammation associated with experimental autoimmune encephalomyelitis (EAE), thereby suggesting a therapeutic potential for recombinant AFP in EAE and other relative autoimmune disorders such as multiple sclerosis (MS) or rheumatoid arthritis[1]. Although this suggestion might be correct, it possibly reflects only one side of the coin. Had AFP role been pro-apoptotic in effector immune cells, this would also result in a protection against cancer development, because prolonged immune responses of such effector cells that exhibit defective apoptosis have been associated with chronic epithelial damage, predisposing for tumorigenesis in many tissues; resistance of T-cells to apoptotic death can extend their lifespan and result in an exceedingly prolonged immune response leading to perpetuation of chronic inflammation with potential tumorigenic effect. For instance, in upper gastrointestinal tract chronic inflammation has been linked to gastric cancer associated with Helicobacter pylori (H. pylori) infection[2]. However**,** AFP-positive gastric cancer has an aggressive behavior; it is strongly associated with hematogenous conditions such as venous invasion, hepatic and brain metastases and aggressive biological factors (p53 abnormalities)[3] Mutations of the p53 gene may be an early event and perhaps work together with H. pylori infection in the pathogenesis of gastric cancer. Mutations of the p53 gene have been thought to upregulate vascular endothelial growth factor (VEGF) and possibly the inducible nitric oxide synthase (iNOS)[2] In this regard, higher expression of VEGF isoform C might be an explanation for the poorer prognosis of AFP-producing gastric cancers[4] Moreover, apart from p53 mutations, H. pylori infection also induces upregulation of VEGF and iNOS expression and subsequent DNA damage as well as enhanced anti-apoptosis signal transduction, thereby contributing to gastric carcinogenesis[2] Taken together, these data suggest that AFP-associated abnormalities of p53 are essential in the early pathogenesis particularly of H. pylori-related gastric cancer, and, moreover, they might be related with the tumor aggressiveness. Of note, loss of heterozygosity and mutations of the p53 also occur commonly in brain tumors[8,9].

Importantly, H. pylori may activate the c-Met, thereby promoting gastric cancer. A higher frequency of c-Met expression is observed in AFP-producing gastric cancer and is associated with decreased apoptosis, high incidence of liver metastases and poor prognosis[2,4]**.** A higher expression of c-Met might be one further explanation for the poorer prognosis of AFP-producing gastric cancers.

Our recent series reported a relationship between MS and H. pylori infection[5] involved in the mentioned carcinogenesis and aggressiveness of upper gastrointestinal malignancies through various mechanisms including indirect associations with AFP. Therefore, further relative studies are warranted, before the therapeutic introduction of the potentially oncogenic recombinant AFP in autoimmune diseases including neurological disorders.

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