Effect of thymosin-alpha1 on the production of nitric oxide by tumor-associated macrophages*

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The present investigation was conducted to study the effect of thymic peptide: thymosinα1 (thyα1) on the activation of tumor associated mϕ (TAM) obtained from mice bearing a transplantable T cell lymphoma of spontaneous origin designated as Dalton's lymphoma, to produce nitric oxide (NO). It was found that in vivo administration of aqueous thymic extract obtained from thymus of normal mice or thyα1 could activate the TAM to produce enhanced amount of NO which was further augmented on in vivo treatment of these TAM by LPS. These observations suggest that thyα1 could prime TAM for activation by second signal of LPS. The study also presents evidence that tumor cell elaborate factors that enhance the effect of thyα1 on TAM for production of NO. This is the first study to show that thyα1 can activate TAM directly even in the absence of LPS, and may, therefore, have clinical significance.

Key words: Tumor-associated macrophages, nitric oxide, Dalton's lymphoma.

Macrophages comprise one of the most important components of the host immune response against neoplasia [13, 22]. Tumor associated macrophages (TAM) are a special type of macrophages that infiltrate the tumor mass and seem to have varying importance in disease progression in different tumors [7, 11]. However, several aspects of the immunobiology of TAM still remain obscure. During tumor progression one or more aspects of the tumoricidal machinery of TAM may be altered in either direction and the outcome depends on the activation state of macrophages and the intrinsic properties of tumor cells [22, 23]. It remains to be established, whether TAM from growing tumors have cytolytic potential that can be enhanced by *in vitro* stimulation [2, 14, 37]. Moreover TAM have been reported to be resistant to activation in response to treatment by LPS [27].

In the recent years, we have attempted to elucidate the effect of the ascitic growth of a transplantable T-cell lymphoma of spontaneous origin, designated as Dalton's lymphoma (DL), on various components of immune system. DL has been selected as a model tumors system, because murine spontaneous tumors resemble human tumors more closely [6, 34]. It was shown that the cytolytic potential of TAM of progressively growing DL gets inhibited [27] along with an inhibition of hematopoiesis and other immune responses [28]. In view of these observations we were interested to screen immunomodulators that could reverse the inhibitory effect of DL growth on the functions of TAM.

In the last decade immunoregulatory activity of a large number of natural and synthetic peptides have been evaluated for their immunomodulatory potential and consequently thymic peptides have gained immense acceptance as immunopotentiators [4, 5]. It has been found that thymosinα1 (Thyα1), a 28 amino acid peptide hormone secreted by thymic stromal cells, is a potent immunomodulator having a wide range of bioactivities [3, 20, 30, 31]. It acts primarily by increasing the ability of T-cells to produce cytokines and by activating monocytes/macrophages [9, 16, 29] Thus the immunostimulating properties of thyα1 have been considered to be useful for improving immuno-

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