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Role of Major Histocompatibility Class I Antigen Expression in Natural Immunity for Tumors Growing in the Brain

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Introduction

It is postulated that the in vivo growth of tumor cells may depend not only on their inherent proliferative capacity but also on their ability to resist immune rejection mechanisms. The latter mechanism may be closely linked to major histocompatibility complex (MHC, H-2 in mice) antigen regulation in tumor-bearing hosts[8]. With aspects of intracerebral immune responses, however, the association of MHC class I antigen expression with in vivo tumorigenicity in the brain has not yet been elucidated. On the other hand, it has been strongly suggested that MHC class I antigen expression is related to natural killer (NK) cell ontogeny[13, 24]. In this context, it has been noted that tumor cells lacking MHC class I antigens are prone to be susceptible to NK cell-mediated lysis[9,15,17-19, 32]. Because most normal cells in the brain have very low level of MHC antigen expression[31], this might have favoured the evolution of specific barriers against the entry of NK cells into the brain.

In this article, the author has briefly reviewed intracerebral natural immunity against tumor development with special reference to MHC class I antigen expression. In addition, our recent experimental results are included that intracerebrally growing H-2-negative tumor cells are not protected from NK cell -mediated rejection response in a mouse system.

Host Immune Resistance

The development of malignant tumors may represent the failure of host resistance to eliminate not only aberrant cells but also neoplastic transformation. Since tumor cells might frequently express surface neoantigens, it has been postulated that they can be recognized as foreign elements and abrogated by the host immunosurveillance system[1,7,29]. Effective immunosurveillance requires not only an immunocompetent host but also appropriate expressions of MHC antigens along with the tumor neoantigens. It has been shown that in many models the immunogenicity of tumors depends upon the situation of MHC class I antigen expression of tumor cells[3,11,14,28]. Experimental transfection of the class I genes into class I-negative malignant cell lines leads to de novo class I antigen expression associated with reduced tumorigenicity and abrogation of metastatic properties. Most of these experiments have been carried out in immunologically competent animals. Thus, it has been supposed that class I antigen expression may lead to effective recognition of the tumor cells by the host immune system. Regarding neoplastic transformation, genetic alterations associated with tumor evolution and progression have been proved, and there is substantial evidence that malignant transformation may lead to aberrant MHC antigen expression in the tumor cells[2,12,27,28].

Immunobiological Significance of MHC Antigen in the Brain

MHC deficiency is typical of almost all resident cells in normal neural and glial cells[31]. Thus, the mechanism might have evolved to prevent rejection of MHC-deficient cells in the brain, either by suppression of NK cell activity or migration of NK cells into the brain, although NK cells can enter local sites of tumor growth in an extracerebral situation[5]. As for mononuclear cell infiltration in the brain, clinical reports have indicated that NK cells were usually absent[22], or found only in low amounts in some tumors[21,23,26], while macrophages and T cells were often distributed throughout the tumor mass[22,23,30]. The fact that most normal cells in the brain have very low MHC class I expression might have favored the evolution of specific barriers against the entry of NK cells into the brain.

Relationship between MHC Antigen and Immunocompetent Cells in the Brain

The MHC class I antigens are important determinants of graft rejection and serve as self-recognition elements for cytotoxic T lymphocyte (CTL)[4,8,29]. In cellular immunity, the class I molecules present endogenous antigens and at the same time act as natural ligands of the CD8 molecule on autologous CTL, thereby mediating cell-cell adhesion and enhancement of antigen-specific receptor binding[6,20,25]. Altered expression of the MHC antigens has been proposed as a mechanism that protects tumor cells from immunosurveillance[10]. Based on animal models, it has been suggested that class I antigen-deficient tumor cells might either have a survival advantage by escaping from a putative attack by autologous CTL or, on the contrary, be more prone to lysis by NK cells, resulting in a survival disadvantage of the class I antigen -negative cells[13]. Such altered MHC class I antigen expression is a well-known phenomenon even in clinical tumor systems, such as malignant melanoma, colorectal carcinoma, B cell lymphoma, small-cell lung carcinoma, and neuroblastoma[2,27].

It has been reported that NK cells are usually absent or are found only in an amounts in some tumors of the central nervous system (CNS)[21,23,26]. Furthermore, it has been demonstrated in a mouse system that H-2 class I antigen-deficient tumor cells are selectively eliminated when inoculated by different extracranial routes, while in the brain such a NK cell-mediated defense mechanism is absent[16]. On the other hand, T cell -mediated immune reactions have access to the brain, although the entry and/or function of the effector cells shows some limitation in the brain[33]. It might be possible that the constitutively low levels of MHC expression set a higher threshold for immunological responses against virally infected or transformed cells in the brain, although once a response is elicited, locally released factors may enhance the MHC expression to ensure optimum conditions for activated T cells. Threrefore, a lack of MHC molecules may facilitate the growth of tumor cells in the brain due to escape from T cell-mediated resistance. Intracerebrally growing MHC antigen-deficient tumor cells may be sheltered from NK cell-mediated rejection. This difference in organ selection between NK cell - and T cell-dependent defense systems may be important for the outcome of viral infections, immunology and immunotherapy of brain tumors, and tissue grafting within the CNS.

Antitumor Natural Immunity in the Brain

A central subject as to intracerebral defense mechanism has been unclarified. This has been proposed to be closely associated with MHC expression on tumor cells.

Our recent experiments using the intracerebral tumorigenicity assay showed that H-2 class I-positive Lym^+, mouse malignant lymphoma cell line, was less tumorigenic than Lym^-, H-2 class-I-deficient subclone derived from Lym^+, in untreated and NK cell -depleted syngeneic mice without pre-immunization[34]. In T cell-depleted mice, however, no difference was found between them, in contrast with the results that in sham control Lym^- was more tumorigenic than Lym^+. No difference in in vitro growth rate or in in vivo intraperitoneal tumorigenicity could be discerned in the two cell lines, suggesting that the inhibition of in vivo intracerebral tumor formation in Lym^+ cells was most probably

mediated through the host immune reactions to tumor cells. In particular, it seems likely that intracerebral tumor suppression was dependent on the high level of cell-surface H-2 class I expression on Lym^+ cells, as compared with cell-surface H-2 negative Lym^- cells. The brain may lack the NK-associated antitumor immunosurveillance found in other parts of the body, where a definite natural resistance exists through the NK-mediated mechanism.

When Lym^+ or Lym^- cells were inoculated into the brain of allogeneic mice, Lym^+ cells were rejected, while Lym^- cells were accepted. When allogeneic mice had received treatment for T cell-depletion prior to intracerebral inoculaton, no rejection was observed in Lym^+ cells. The results suggest that the natural immunity in the brain may be T cell-dependent. It was also noted that Lym-cells with an irreversible H-2 defect were not rejected even if inoculated together with Lym^+ cells into the brain. This indicates that the final abrogation of the tumor cells in the brain may be dependent on H-2 class I expression on the tumor cells. Our current study suggests the absence of NK cell-mediated resistance in the brain, although the reason remains unclear. Further investigation will be warranted.

Conclusion

It can be concluded that the MHC class I-positive tumor cells grafted into the brain may be rejected by CTL in an MHC-dependent manner, while MHC-negative tumor cells can escape from T cell-mediated immunosurveillance and grow progressively in the brain, due to absence of intracerebral natural immunity mediated by NK cells. Furthermore, it is suggested that in the immunologically privileged brain, the levels of MHC class I antigen expression on tumor cells may contribute mainly to the in vivo tumorigenicity, regardless of whether a high level of expression and/or amplification of tumor-related oncogenes might be closely linked to in vitro tumor cell proliferation and cellular differentiation.

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