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Melanoma Immunotherapy

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1. Introduction

Although the mortality due to melanoma or malignant mutated pigment cell cancer has begun to stabilize in developed country (1, 2), the disease shows, however a substantial increased incidence which, in term of public health, represents a high burden (3-5). As well known, among the risk factors leading to melanoma there is exposition to solar ultraviolet radiation associated to sensitive genetic background (6-9). Numerous reports have shown that important key genes such as MC1R or melanocortin-1 receptor, BRAF, NRAS as well as IDH1 were mutated in melanoma (10-16). Once metastases occur, the rate of patients'5 year survival is low (17), at this stage, it was shown that melanoma develops a resistance to current chemotherapy associated to high level of apoptosis inhibition (18, 19). Treatment is becoming difficult, useless and even futile. Although new generation of drugs is in development aiming to target mutated gene expression product sustaining tumor cell proliferation, i.e., BRAF (20) there is an urgent need for novel therapeutic approaches such as cancer immunotherapy involving immune effectors specifically activated for killing tumor cells.

2. Stimulating antimelanoma immune effectors

Efforts toward development of cancer immunotherapy have mainly focused on the possibility to vaccinate patients for obtaining specific immune response against their own cancer. The characterization of numerous tumor associated antigens or TAAs, especially in the context of melanoma with melanoma associated antigens (MAAs) such as gp100, MAGE-1, MAGE-3, MART-1 as well as tyrosinase has allowed to derive epitopes used for inducing CTLs (cytotoxic T lymphocytes) (21-28). In most of the case, the tumor associated antigens which belong to the group of differentiation antigens shared with normal tissue, are less immunogenic than those derived from pathogen (virus, bacteria). Thus several procedures were used in order to increase the MAA's immunogenicity such as amino-acid sequence alteration, cytokine boosting. As well known, the immunogenic peptide, in general, harboring anchor residues that bind to the MHC (major histocompatibility complex) antigen presenting molecule forming a stable complex that is essential for immune cognate recognition (29). As an example, the human MHC class I, HLA-A2 bind with high affinity peptides with either leucine/methionine at position 2 or valine at position 9 in the 9-10 amino-acid sequence. Thus a substitution of anchor residues at the indicated position (2 and/or 9) by high affinity binding ones will render the modified peptide, i.e.,

gp100 209-217 2M (IMDQVFSV) more immunogenic than the native sequence, i.e., gp100 209-217 (ITDQVFSV) (30). In clinical trials, vaccination of patients with the modified peptide, gp100 209-217 2M has been shown to increase the number of CTL precursors recognizing not only the modified peptide, but also the native one (31). It is worth to note that, although alteration in amino-acid sequence has led to increasing the immunogenicity of the tumor associated antigenic peptide, other factors were necessary to achieve objective clinical response, i.e., the use of adjuvant and cytokine. Thus, the oil-based montanide ISA 51 or IFA (incomplete Freund's adjuvant) (32,33) being shown to stimulate immune response was frequently used (34,35) contributing to the overall T cell immune stimulation. However, as reported by Rosenberg and colleagues, the immune response leading to objective clinical response was observed only when patients received also IL-2 along with the vaccine (31). Likewise, Weber and colleagues (36), Lee and colleagues (37), have shown the implication of GMCSF (granulocyte-macrophage-colony stimulating factor) and IL-12, respectively as boosting factors that stimulated CTL response to melanoma peptides gp100, tyrosinase and MART-1.

3. Immune and clinical response to melanoma vaccination

Results from numerous vaccine trials using melanoma peptides in patients with either primary or metastatic resected tumors showed the presence of CTLs as measured by the release of IFN-gamma (ELISA, Elispot tests), Cr 51 cytotoxicity assay, TCR specificity assay with tetramer analysis, skin test, among other assays. However, as far as could be observed, the generated CTLs from immunization approaches were variable in their antimelanoma potency which could be ranged, in the case of gp100 vaccine, from cytotoxic only to modified peptide pulsed target, to cytotoxic to both native and modified peptide sensitized target but not melanoma, or recognizing HLA matched melanoma peptide pulsed target and finally recognizing melanomas HLA-A2+ gp100+ (38). Furthermore, the immune response did not always correlate with tumor regression, although there were indications that positive immune response obtained in ELISA and Elispot assays correlated better with prolonged relapse-free survival (35). Overall, the lack of correlation between the high proportion of positive immune response among immunized melanoma patients and objective clinical effects could be explained by the difficulty in obtaining CD8+CTLs with specific high avidities. Another possibility is that tumor cells might express low number of specific epitopes on their cell surface, or simply down regulated the MHC I presenting antigenic peptide. Another approach developed by the group led by Rosenberg consisting to isolate reactive immune effectors infiltrating the tumor (TILs or tumor infiltrating lymphocytes) which have shown to produce objective cancer regression in treated patients (39-42). The prior lymphodepletion by treatment with cyclophosphamide and fludarabine has probably enabled the persistence and the function of adoptive transferred cells. The onset of autoimmune melanocyte destruction that accompanied cancer regression is considered as the hallmark of efficient reactive effector cells that have targeted also normal tissue expressing melanocyte differentiation antigen. The efficacy of T cell transfer as reported by the Rosenberg's group in comparison with the active immunization of patients with melanoma could be explained by the fact that reactive T cells were already selected in the work of the former and the lymphodepletion has, in addition, contributed to disrupt and overcome some tolerogenic and normal homeostatic regulation.

4. Targeting IGF-1 based melanoma immunotherapy

4.1 IGF-1 as target in melanoma immunotherapy

Beside the above strategies that are essentially based on activation of immune effectors through antigenic differentiation peptides, other strategy has been explored by means of gene transfection aiming to increase tumor immunogenicity in disrupting its immune tolerance/suppression. There were for example experimental models in which gene coding for either immunogenic foreign protein such as OVA (egg albumin) or MHC-I were introduced into tumor cells making them sensitive to immune effectors (CTLs)(43-48). In the following chapter we reported results concerning the strategy that consisted to inhibit melanoma autocrine growth factor IGF-1 expression and its consequences upon the recruitment of antimelanoma immune effectors. The strategy is thus based on the use of antisense episomal vector as well as specific antibody targeting melanoma IGF-1 expression. Concerning the experimental model, the B16 melanoma cell line originated from the mouse strain C57Bl/6 (H-2b) was used (49). There are several variants derived from the B16 cell line. The most studied melanoma variants are the highly metastatic B16-F10, BL6 and the subline B78H1 (50-52). The latter one is mainly devoid of TAP2 gene as well as MHC-I K b and D b which are weakly expressed in the formers and whose expression is inducible by IFN-γ (interferon gamma).

Although widely used the B16 melanoma was subject to critics according to which it was not a good experimental model due to differences with the human counterparts, particularly the lack of some key mutations such as those found in *PTEN* and *BRAF* (53,54). In general, cancer cells are heterogeneous with constant developmental evolution and adaptation, leading to regular acquisition of several new emerging mutant phenotypes (55,56), it is therefore difficult to find out a best defined one model for studying all complex aspects relevant to the cancer biology. Nevertheless, approaches through a well known model would allow to analyze and dissect the mechanisms underlying the deregulated growth of the relevant malignant cancer type. In the present work we focused on IGF-1 expressed in melanoma which is known as the most prominent growth factor produced by the majority of cancer types. Thus, as a pleotrophic growth factor, IGF-1 plays an essential role in cellular proliferation and apoptosis inhibition (57,58). Therefore, targeting IGF-1 appeared as an effective strategy for the control of tumor development and tumor invasiveness. This strategy had been already applied to experimental models of glioma and hepatocarcinoma, leading to prevent the tumorigenicity of the former and rendering the latter less tumorigenic (59,60). In these reported studies the control exerted on tumor development as well as on tumor rejection was undoubtedly due to the action of immune effectors, since it was reported the presence of CD8+ T cells at the site of tumor rejection.

4.2 In vitro analyses of inhibited IGF-1 melanoma cells

As stated above, the two procedures used for inhibiting IGF-1 expression in B16 melanoma cells were transfection of tumor cells with antisense episomal vector as well as treatment with specific antibodies. The IGF-1 episomal vector harboring IGF-1 antisense cDNA was constructed as depicted in the work reported by the group led by J.Ilan from Case Western Reserve University, Cleveland, Ohio (USA) (61). Briefly, the expression vector construct, a gift from Dr Ilan, incorporated EBV (Epstein-Bar virus) replicative signals, an IGF-1 cDNA transcriptional cassette, a gene encoding nuclear antigen 1 and a metallothionein-I promoter. This construct is episomal and drive extrachrosomal

replication. The vector was transfected to B16 melanoma cells by electroporation giving rise to subclones selected according to their resistance to the selective pressure of hygromycin B. It was shown that activation of the transgene leading to extinguish IGF-1 expression did not affect the viability of transfected melanoma cells (62). Concerning the treatment using specific antibodies, the B16 melanoma cells were submitted to anti-IGF-1 antibodies that were made, in the present work, from goat and available commercially (Abcys, France). Two treatment cycles in the presence of heterologous complement (rabbit) were performed and the cells that have survived were subcloned. The two IGF-1 inhibitory procedures have led to obtention of subclones showing abrogated IGF-1 expression as ascertained by immunocytochemical assays (62). Thereafter, the inhibited IGF- 1 melanoma cells were submitted to analyses concerning mainly their morphology as well as the expression of their cell surface molecules in comparison to parental cells. It was shown that the inhibited IGF-1 B16 did not reveal noticeable difference with parental cells relevant to their morphology, their in vitro growth in culture as well as their adherence properties. It is worth to note that results reported from studies of C6 glioma have indicated a slight difference in the morphology between wild-type and transfected cells, at least in the early period of cell culture (61). Concerning the expression of cell surface molecules, studies were focused on those involved in immune activation, mainly the MHC-I and B7.1, as well as in cellular interactions such as the family members of integrin and tetraspanin molecules. From the results obtained, it was shown that the expression of molecules known for their implication in the immune activation processes remained unmodified (62). The results obtained were thus different from previously observed when glioblastoma C6 and hepatoma LF were transfected with antisense IGF-1 vector. Indeed, in these studies, the IGF-1 modified cells exhibited either an upregulation of MHC-I and B7.1 expression (glioma C6 cells) (63) or a strong increase of MHC-I expression (hepatoma LF cells) (62).

Among the group of molecules involved in cellular interaction, an alteration in the expression of the tetraspanin CD9 but not CD81 was essentially observed. The expression of the integrin α4/CD49d remained unchanged. The fact that only one member of the tetraspanin family molecules was affected is of interest and suggested that the tetraspanin CD9 and CD81 followed different pathways in their expression. It is worth to note the implication of CD9 but not CD81 in the cancer process as reported elsewhere (64).

4.3 In vivo tumor development of inhibited IGF-1 melanoma cells

The potential of inhibited IGF-1 B16 modified melanoma cells to develop into solid tumors in vivo were assessed (62). 25X1000 cells from either inhibited IGF-1 or parental cells were thus subscutaneously injected to C57BL/6 mice, their syngeneic host. The development of injected cell suspensions into solid tumors was followed up by regular examination and measures using a caliper. It was shown that solid tumors were developed in syngeneic hosts with a delay when modified B16 cells inhibited in their IGF-1 expression were injected as compared to the parental counterparts. The difference was significant and resulted in tumors with a mean size smaller than that of parental cells in the interval of time starting from the cell injection to the first apparition of lethal tumors which were observed in all recipients of injected parental cells. On the other hand, a proportion of 40-50% of recipients injected with modified B16 cells (IGF-1 inhibited) survived free of tumor for more than three months while no survival was observed among the recipients of parental cells.

4.4 Characterization of immune effectors stimulated by modified melanoma cells exhibiting inhibited IGF-1 expression

The fact that modified (IGF-1 inhibited) B16 cells developed solid tumors in syngeneic hosts with an aggressiveness lesser than parental cells suggested the presence of effector elements in host organisms controlling the outgrowth of modified cells (62). Since there was no difference between parental and inhibited IGF-1 B16 modified cells related to their in vitro cell culture expansion and their in vivo growth in immunocompromised recipients (NOD-SCID mice) (Nguyen et.al., unpublished results), it was assumed that tumor development from modified B16 cells in syngeneic host was regulated by adaptive immune effectors. In order to characterize the immune effectors controlling in vivo tumor development, experiments were performed using melanoma cells, either from inhibited IGF-1 or parental type, for vaccinating syngeneic immunocompetent hosts (65). The two types of melanoma cells were first blocked by mytomycin C treatment or by several frozen and thawed cycles. The blocked cells were subsequently injected to C57Bl/6 mice in vaccination purpose. The spleen cells and the sera from vaccinated animals harvested 10-15 days after were assessed for their effects upon B16 tumor cells in comparison to that of control untreated animals . The results obtained with the serum collected from mice vaccinated with parental cells showed no difference with the control serum from untreated animals. On the contrary, the serum collected from mice vaccinated with modified (IGF-1 inhibited) cells revealed the presence of antibodies that recognized not only modified, IGF-1 inhibited B16 cells but also their parental counterparts. This aspect was essentially observed in cytometry (FACS) analyses as well as in cytotoxic assays. Thus, in cytometry analyses the mean fluorescence obtained with serum from mice vaccinated with modified cells was 7-9 fold higher as compared to that obtained with serum from mice injected with parental B16 cells which was not different to the results from normal serum. Moreover, only serum collected from mice vaccinated with modified B16 cells exhibited cytotoxic activities against melanoma cells in the presence of heterologous (rabbit) complement, while practically no cytotoxic effects were observed with serum from mice injected with parental cells. Concerning the cellular effectors, in vitro cytotoxic assays showed that spleen cells harvested from mice injected with modified, IGF-1 inhibited B16 cells were able to kill melanoma cells, either of parental or modified type. On the contrary, melanoma cells were not affected by the presence of spleen cells from mice injected with parental cells as well as with spleen cells from normal untreated mice (65).

These immune, humoral and cellular effector elements were also analyzed for their effects on the in vivo tumor development. In these in vivo assays, serum or spleen cells from mice vaccinated either with parental or modified, inhibited IGF-1 cells were injected together with melanoma cells to syngeneic hosts. Results obtained have shown that only spleen cells but not the immune serum from mice vaccinated with modified, IGF-1 inhibited B16 cells were able to control the tumor development in syngeneic hosts. No effect on tumor growth was observed with the spleen cells from mice vaccinated with parental cells or spleen cells from control untreated mice as well as their serum (65, 66). The discrepancy between the in vitro and in vivo, humoral and cellular results concerning the case of mice vaccinated with modified-inhibited IGF-1 cells could be explained by the cell surface movement or capping phenomenon which could mask the antibody to ADCC/complement fixing lysis. Another alternative could be relevant to the short half-life of antibody molecules compared to cellular effectors that would persist longer in the syngeneic host organisms.

Experiments were further performed for characterizing the active anti-tumor cell population(s) from spleen cells of mice vaccinated with modified, IGF-1 inhibited B16 cells. The above immune spleen cell suspension was thus submitted to negative selection by means of protein A - sepharose beads coated with specific antibody to CD4, CD8, NK (NK1.1), CD25, Ig (Immunoglobulin) and B220. It was shown that the anti-tumor activity was affected when spleen cell population was incubated with anti-CD8 antibody coated beads and removed from the cell suspension. The treatment of spleen cell suspension with other antibody-coated beads did not affect its anti-melanoma activity, indicating that spleen CD8+ T cells were the main immune effectors controlling in vivo melanoma development (66).

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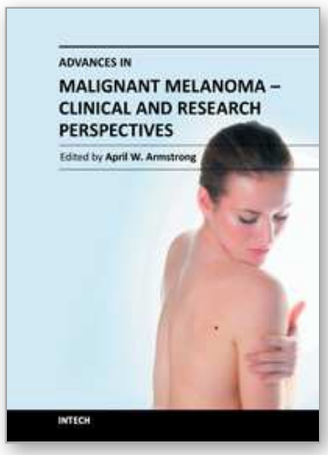

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This book titled Advances in Malignant Melanoma - Clinical and Research Perspectives represents an international effort to highlight advances in our understanding of malignant melanoma from both clinical and research perspectives. The authors for this book consist of an international group of recognized leaders in melanoma research and patient care, and they share their unique perspectives regarding melanoma epidemiology, risk factors, diagnostic and prognostic tools, phenotypes, treatment, and future research directions. The book is divide into four sections: (1) Epidemiology and Risk Factors of Melanoma, (2) Clinical Phenotypes of Melanoma, (3) Investigational Treatments for Melanoma and Pigmentary Disorders, and (4) Advances in Melanoma Translational Research. This book does not attempt to exhaustively cover all aspects of the aforementioned topics. Rather, it is a compilation of our authorsâ€™ pearls and unique perspectives on the relevant advances in melanoma during the recent years.

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