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Co-operation of Innate and Acquired Immunity for Controlling Tumor Cells

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1. Introduction

The body is composed of various types of cells that unite in harmony to live in the natural environment. Viral infections, toxic products, and environmental stresses may affect the cells to initiate transformation for the development of tumors, an uncontrollable and unfavorable state of cells. Such a tumor state of cells is closely watched by the internal immune-surveillance system that generally controls or eliminates them to maintain the harmony of the body.

The internal immune-surveillance system is composed of two distinct parts; an innate immune system predominantly located on the surface areas of the body, such as the skin or mucosal compartments, and an acquired/adaptive immune system found mainly in systemic compartments, including circulating blood, lymph nodes, spleen, and various organs (Medzhitov and Janeway, 1997a) (Fig. 1). The cells of the innate immune system find and fight foreign bodies intruding from the outside, such as viruses and bacteria, through their pattern-recognition receptors (PRRs) (Medzhitov, 2007), such as Toll-like receptors (TLRs) (Akira et al., 2001) and C-type lectin receptors (CLRs) that recognize pathogen-associated molecular patterns (PAMPs) (Medzhitov and Janeway, 1997b), although they do not have any specific memories of foreign bodies. In contrast, the acquired immune system will respond to foreign elements only when competent cells of the acquired system recognize them specifically through their receptors established via gene-rearrangements (Palm and Medzhitov, 2009). Among these acquired receptors, a T-cell receptor (TCR) can specifically recognize foreign antigens as a specific structural component composed of protein-derived amino acids presented particularly by self-restricted antigen-presenting molecules, termed major histocompatibility complex (MHC) (Takahashi, 2003)

Although the precise mechanisms remain to be elucidated, such specific memories mediated through TCRs are instructed by innate cells, particularly dendritic cells (DCs), which are key cells to present antigenic information though their MHC together with co-stimulatory molecules that will promote memory formation via gene-rearrangements in acquired T cells. Therefore, innate DCs have the ability to capture tumor-derived antigens, processed them into antigenic fragments, and present the antigenic fragments in association with their MHC and co-stimulation molecules (Azuma et al., 1993; Chen et al., 1992), such as B7-1 (CD80), B7-2 (CD86), or CD40, to establish TCR-mediated antigen-specific memories in acquired immunity (Fig. 2).
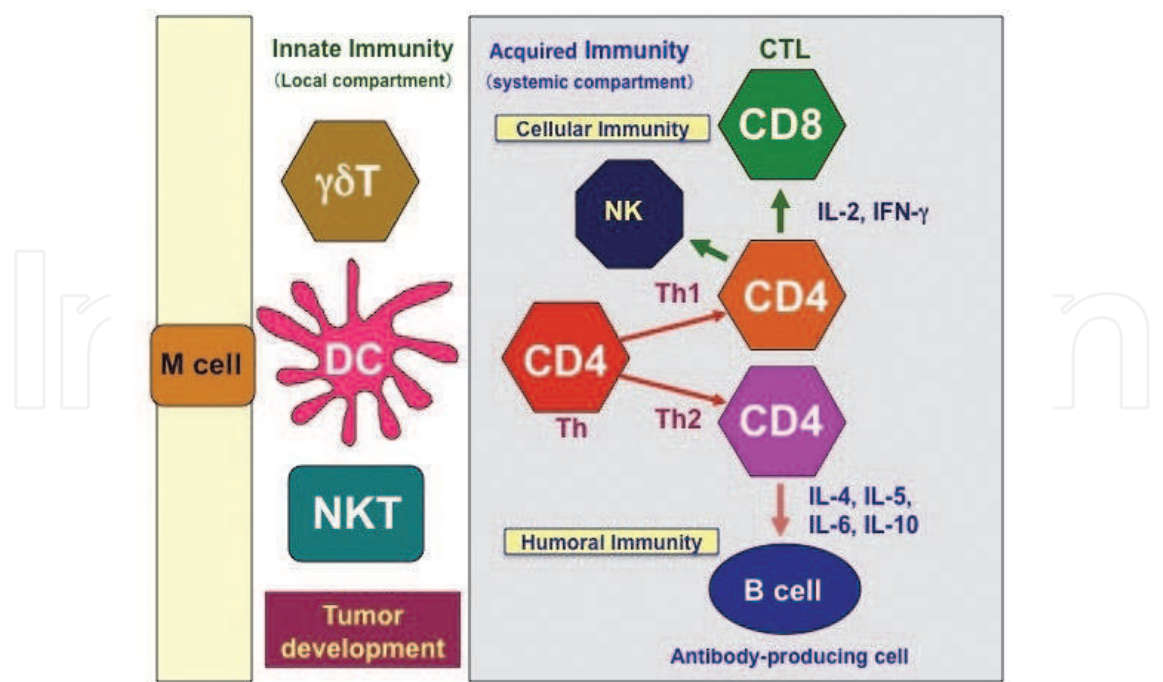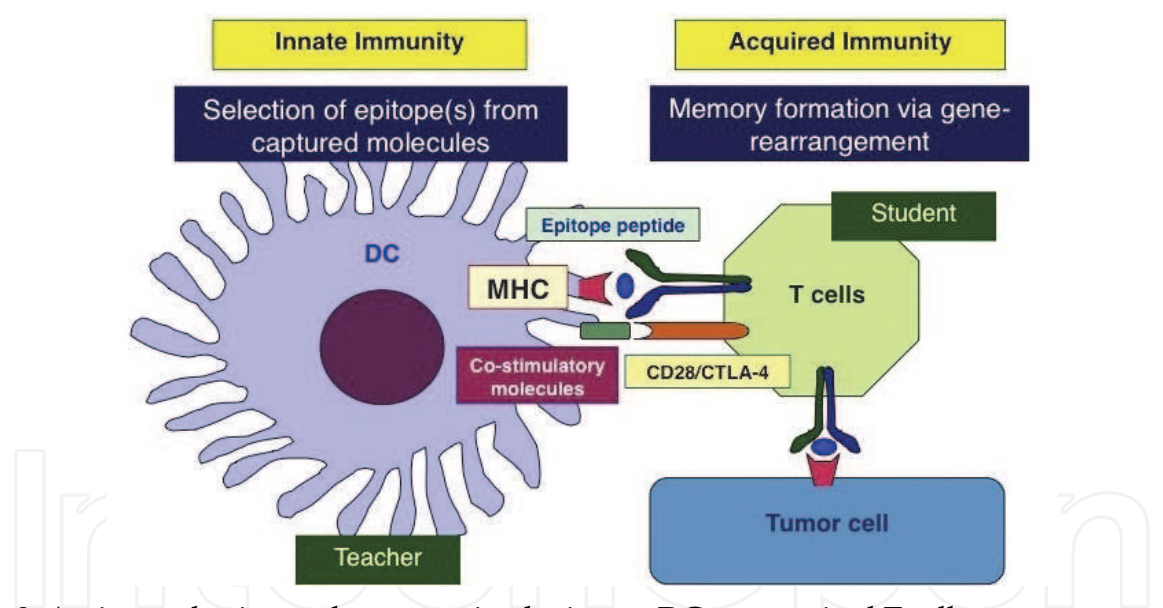
Fig. 1. Innate immunity and acquired immunity.

Fig. 2. Antigen selection and presentation by innate DCs to acquired T cells.

Two distinct MHC molecules are expressed on the surface of antigen-presenting cells, class I and class II MHC. In general, class I MHC molecules can present processed fragments of internally produced tumor-gene or virus-gene-derived antigens to CD8+ T cells, whereas class II MHC present processed fragments of externally captured antigens to CD4+ T cells (Takahashi, 1993) (Fig. 3).

Among TCR-mediated specific acquired immunity, class I MHC molecule-restricted tumor-peptide-specific immunity by CD8+ cytotoxic T lymphocytes (CTLs) is particularly important in the elimination of tumor cells and both class I MHC molecule-associated antigenic stimulation and co-stimulatory signals on the same antigen-presenting cells (APCs) are

required to elicit such CD8^{+} CTLs; however, in general, tumor cells that present tumor-derived antigenic peptides in association with their class I MHC do not express appropriate co-stimulation molecules and thus they cannot induce tumor-specific CD8^{+} CTLs.
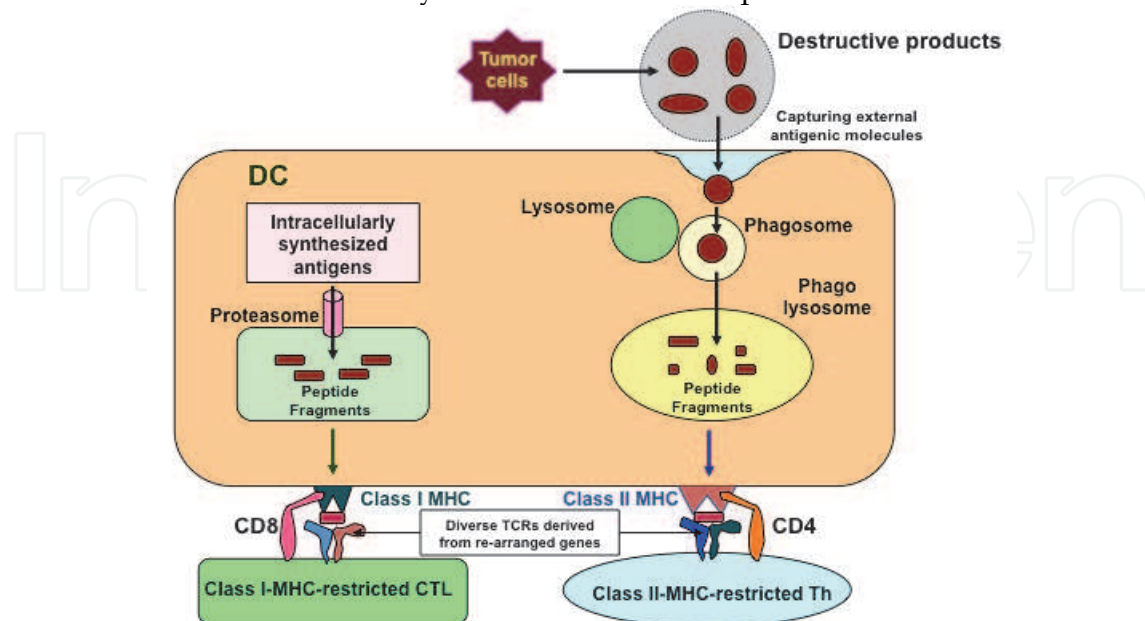

Fig. 3. Two distinct antigen presentation pathways mediated in DCs via class I and class II MHC molecules.

In addition, DCs will not usually become tumor cells and thus are unable to present tumor antigens in conjunction with their class I MHC, despite expressing suitable co-stimulation molecules for the elicitation of tumor-specific CD8^{+} CTLs.

On the basis of our recent findings (Moriya et al., 2010), this chapter propose a new direction for the establishment of tumor immunotherapy to generate tumor-derived epitope-specific class I MHC molecule-restricted acquired CD8^{+} CTLs against tumors by selective activation of DEC-205^{+} DCs that have the ability to process and cross-present antigenic fragments from externally captured tumor-derived products via class I MHC as well as innate effectors such as NKT cells and γδ T cells through their CD1 molecules (Takahashi, 2010).

2. Innate and acquired effectors against tumor cells

Tumor cells originate from normal functional cells, like melanoma from melanocytes, via several transformation steps, which can be classified into two types; early transformation steps initiated by stress-related substances and late transformation steps that generate mutated genes to gain uncontrollable proliferative capacity. The stress-associated products are expressed on the cell surface in association with MHC class I chain-related A (MICA) and MICB molecules, which are composed of a similar structural pattern of class I MHC. These MICA/MICB-associated compounds are recognized by NK group 2D (NKG2D) receptors of activated innate effectors, such as natural killer (NK) cells, natural killer T (NKT) cells, and γδT cells, bearing invariant receptors produced without gene-rearrangements (Higuchi et al., 2009). These innate effectors recognize early transformed tumors via NKG2D receptors and eliminate them. Also, MICA/MICB expressing tumor cells usually show down-modulation of class I MHC that will stimulate NK cells to eliminate them (Suarez-Alvarez et al., 2009).

In contrast, mature tumor cells with mutated genes and expressing tumor-gene-encoded antigenic peptides on their surface in association with class I MHC molecules can be specifically recognized and eliminated by acquired CD8+ CTLs. Thus, stress-associated early transformed tumor cells appear to be regulated mainly by innate effectors, while mature tumor cells with specific structural mutations with high proliferative capacity can be specifically controlled by acquired CD8+ CTLs in a class I MHC molecule-restricted manner. Taken together, internally transformed tumor cells gained uncontrollable proliferating capacity can be recognized and regulated by both innate and acquired effectors (Fig. 4).
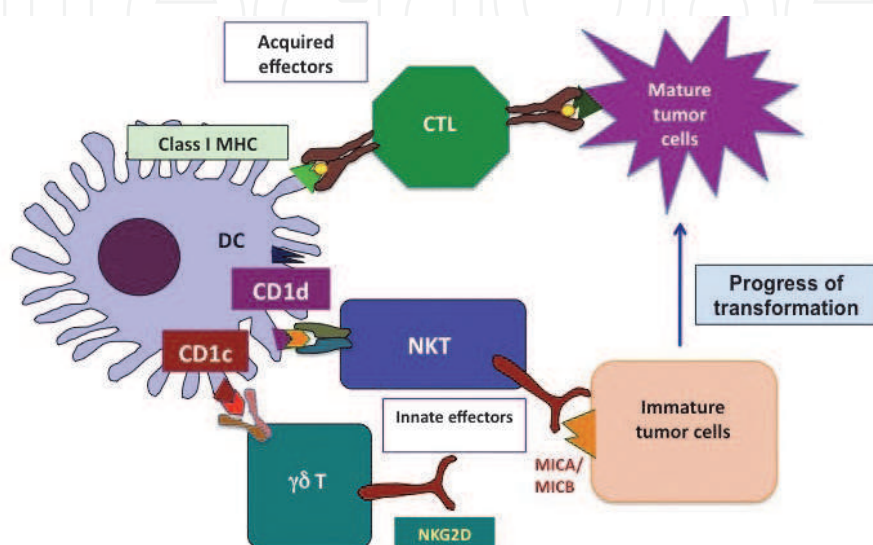

Fig. 4. Immune control of immature and mature tumor cells.

3. Antigen-presenting molecules on DCs

Induction of these innate and acquired effectors seems to be regulated by DCs via various antigen-presenting molecules. Innate immunity is chiefly regulated via species-restricted CD1 antigen-presenting molecules and acquired immunity is controlled via individually restricted MHC molecules on DCs. CD1 molecules are further divided into four classes, CD1a, CD1b, CD1c, and CD1d. These CD1s have been found to present lipid/glycolipid antigens to T cells bearing relatively invariant αβT-cell receptors (TCR), most of which are conserved among species (Barral and Brenner, 2007; Cohen et al., 2009). For example, highly conserved CD1d molecules present α-galactosyl ceramide (α-GalCer) to NKT cells of their own species (Saito et al., 2005). Indeed, human NKT cells generally express unique combinations of TCRs that consist of an invariant Vα24 chain preferentially paired with a Vβ11 (Dellabona et al., 1994), while murine α-GalCer-reactive CD1d-restricted NKT cells express invariant Vα14 paired with various Vβ combinations (Gui et al., 2001).

In contrast to species-restricted CD1 antigen-presenting molecules, both class I and class II MHC molecules are highly diverse among individuals as self-restricted elements presenting internally processed peptides as antigens, which can be recognized by the same MHC molecule-bearing αβTCR-expressing T cells with antigen-specificity established by intracellular gene rearrangements. Such gene rearrangements for the establishment of T cell-mediated acquired immunity can be initiated through the combination of antigen-loaded MHC molecules plus appropriate co-stimulatory signals on DCs, although the induction of CD1-associated T cells does not require such co-stimulatory signals. Thus, co-stimulatory

signals appear to be required for the development of MHC molecule-restricted highly specific acquired immunity (Nakatsuka et al., 1999). Generally, CD8αβ-positive T cells recognize the processed epitope peptide from internally synthesized proteins presented by class I MHC molecules, whereas CD4-positive T cells recognize epitope peptide from externally captured proteins in association with class II MHC (Dustin, 2009). The structures of the two distinct groups of antigen-presenting molecules, CD1 and class I MHC, closely resemble each other, having three regions of α–chains (α1, α2, and α3) with non-covalently bound β2-microglobulin that may regulate the antigen-binding capacity of the presenting molecules (Kozlowski et al., 1991). However, although CD1-encoding genes are highly conserved and their structures are shared among species with limited polymorphism (Couedel et al., 1998), the class I MHC-encoding gene is highly diverse among individuals. So far, it has been reported that most innate NKT cells can be activated through CD1d and some γδT cells are activated through CD1c molecules on DCs (Cohen et al., 2009). Moreover, we have recently observed that live bacillus Calmette-Guerin (BCG)-activated DCs elicit innate effectors, such as NK cells, NKT cells, and γδT cells, to inhibit the growth of bladder carcinoma via IL-12 secretion (Higuchi et al., 2009). Collectively, DCs have the ability to manipulate innate effectors through CD1s and cytokines, as well as acquired effectors via MHC molecules to control internal tumors.

4. DC subset and "cross-presentation"

Recently, it has been demonstrated that two non-overlapping subsets of DCs are arranged to regulate internal immune responses *in vivo*; 33D1 (recognizing dendritic cell inhibitory receptor-2 (DCIR2))-positive and DEC-205-positive DCs (Dudziak et al., 2007). It has also been reported that *in vivo* targeting of DEC-205 with either poly(I:C) (Trumpfheller et al., 2008) or an antibody specific for DC-NK lectin group receptor-1 (DNGR-1) (Sancho et al., 2008) induced dominant Th1 immunity or potent CTL responses via cross-presentation, respectively. As indicated in Fig 5, it has turned out that the most suitable CTL epitope peptides within externally captured antigenic proteins are selected to present in association with class I MHC in DEC-205-positive DCs via cross-presentation (Moriya et al., 2010).

We have shown that such cross-presentation, the shift of the antigen-presentation pathway from the class II MHC to class I MHC processing route for externally captured antigenic proteins, can be achieved by a bark-derived saponin-associated adjuvant, such as ISCOMs (Takahashi et al., 1990), cholera toxin (CT) (Wakabayashi et al., 2008), and BCG (Higuchi et al., 2009). We have also demonstrated (Fujimoto et al., 2004) that TLR3-signaling of DCs, previously loaded antigenic proteins, by double-stranded RNA, polyriboinosinic polyribocytidylic acid (poly(I:C)), which reflects a natural genetic product from a variety of viruses, can generate the cross-presentation.

These results suggest that selective stimulation of DEC-205$^+$ DCs *in vivo* may elicit effective acquired CD8$^+$ CTL responses through Th1 dominancy by which protective immunity against tumors will be achieved even in the absence of externally added tumor antigens. We have recently established 33D1$^+$ DC-depleted C57BL/6 mice obtained by treatment with 33D1-specific monoclonal antibody (Moriya et al., 2010). As expected, 33D1$^+$ DC-depleted mice, implanted with syngeneic B16-F10 melanoma cells into the dermis, showed apparent inhibition of already established tumor growth *in vivo* when subcutaneously (sc) injected with LPS after tumor implantation, in which serum IL-12 secretion that may be mediated by the remaining DEC-205$^+$ DCs was markedly enhanced upon TLR4 signaling (Moriya et al., 2010). Unexpectedly, LPS-stimulated 33D1$^+$ DC-deleted tumor-bearing mice apparently produced H-2K^b-restricted epitope-specific CD8$^+$ CTLs among tumor infiltrating

lymphocytes (TILs) against already established syngeneic tumor cells (Moriya et al., 2010). These findings indicate the importance and effectiveness of selective targeting of a specific subset of DCs, such as DEC-205^{+} DCs, for the activation of tumor-specific class I MHC molecule-restricted CD8^{+} CTLs without externally added tumor antigen stimulation *in vivo*.
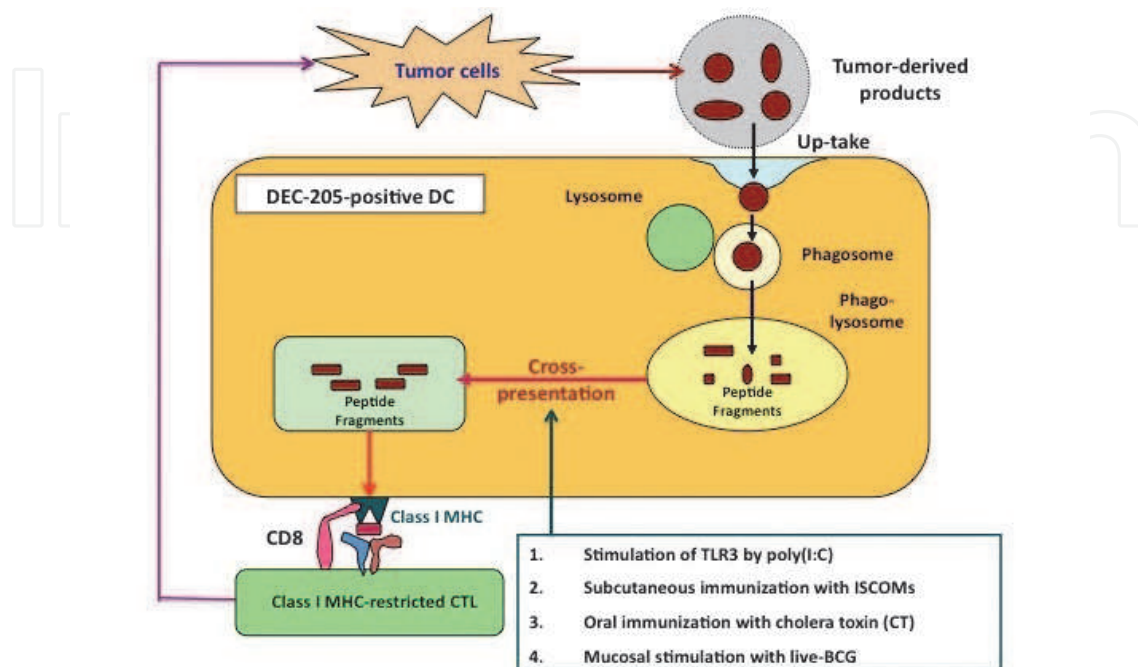

Fig. 5. New direction for tumor immuno-therapy.

5. Concluding remarks: A new direction for tumor immunotherapy

Because tumor epitope-specific CD8^{+} CTLs can be primed *in vivo* by immunization with epitope peptide-pulsed syngeneic DCs (Takahashi et al., 1993), most of the present works for the establishment of cancer immunotherapy have focused on identifying tumor-derived epitope peptides in each tumor; however, tumor-derived specific epitope peptides are generally very difficult to determine for most tumors because the structure of each epitope and its MHC cassette is highly diverse among individuals.

Here, we would like to propose a new, promising strategy for the development of cancer immunotherapy; selective activation of DEC-205^{+} DCs *in vivo*. It should be noted that innate DEC-205^{+} DCs do not have memories and thus, repetitive intermittent stimulation is required to carry out this procedure. By this method, selectively activated DEC-205^{+} DCs recognizing newly appeared tumor cells capture antigenic molecules and present their antigenic epitopes in association with class I MHC via cross-presentation, and the presented epitope will prime acquired tumor-specific class I MHC molecule-restricted CD8^{+} CTLs that specifically recognize tumor cells with mutated genes and attack them. As far as we have examined, ISCOMs, CT and BCG have the capacity to selectively stimulate DEC-205^{+} DCs *in vivo*. Indeed, repetitive immunization with adjuvant alone shows apparent inhibition in the growth of syngeneic implanted tumors (Wakabayashi, A., Nakagawa, Y., Date, T., Tomita, Y., Shimizu, M, and Takahashi, H.; manuscript in preparation).

In addition, as has been shown above, live BCG has the ability to activate innate effectors such as NK cells, NKT cells, and γδT cells to suppress the growth of early transformed tumors expressing MICA/MICB and stress-related substances via NKG2D (Higuchi et al.,

2009). These results strongly suggest that we can manipulate appropriate immunity to control tumor cells by repetitive stimulation of DEC-205+ DCs with a BCG-derived substance. Now we should recall the name of Chisato Maruyama (1901-1992), a professor of the Department of Dermatology as well as the past President of Nippon Medical School in Japan, who had noticed that there were a very low number of cancer patients suffered from tuberculosis and established special substance from *Mycobacterium tuberculosis* as a cancer vaccine, named the "Maruyama Vaccine (SSM; special substance of Maruyama)" in 1944. The SSM has been widely used, particularly for various cancer patients in Japan; however, the actual mechanism of the SSM has been unknown until now. Thus, although a number of cases with excellent effects on cancer regression by SSM have been reported, many doctors are still suspicious of the effect of SSM. Here, it is proposed that new adjuvant therapy should be considered, including BCG or SSM that will activate internal innate immunity, particularly DEC-205+ DCs.

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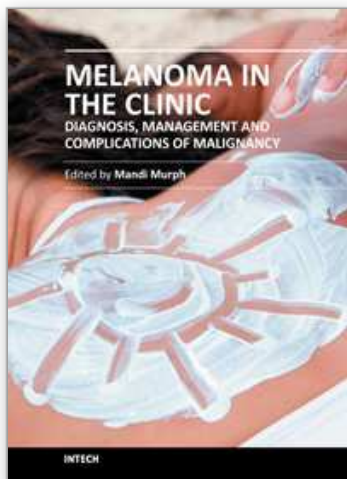
Melanoma in the Clinic - Diagnosis, Management and Complications of Malignancy
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This book provides an excellent overview of how melanoma is treated in the clinic. Since oncologists and clinicians across the globe contributed to this book, each area also explores the unique burdens that geographical areas experience from melanoma subtypes and how these are treated in different settings. It also includes several chapters that illustrate novel methods for diagnosing melanoma in the clinic using new technologies, which are likely to significantly improve outcomes. Several chapters cover surgical techniques and other present very rare or challenging clinical cases of melanoma and how these were treated. The book is geared towards informing clinicians and even patients how melanoma arises, what tools are available and which decisions need to be made by patients and their families in order to treat this devastating disease.

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