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Current Insight Into the Metastatic Process and Melanoma Cell Dissemination

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1. Introduction

Tumour metastasis is the primary cause of death in cancer patients, and cutaneous melanoma is one of the most highly metastatic cancers. While early stage melanomas are almost always curable, despite new and promising treatments (Flaherty et al., 2010; Hodi et al., 2010), advanced unresectable melanomas (Stage III and IV) have a much worse prognosis (Shivers et al., 1998). Similarly, once uveal melanomas have metastasized, they are irretrievably lethal (Kivela et al., 2006).

Until recently, tumour cell dissemination was thought to be a late event in cancer progression (Fearon and Vogelstein, 1990). But the advent of sensitive and reliable techniques for detecting circulating tumour cells has revealed that tumour cells can disseminate long before the primary tumour reaches a clinically detectable size. A growing body of convergent studies, including those from our laboratory, confirms this finding in both mice and humans.

If some cancer cells disseminate before diagnosis and if metastases develop from these disseminated cancer cells, how can the treatment of the primary tumour impact disease progression? Or might it be more efficient to focus therapeutic intervention on the control of the disseminated cancer cells?

This new paradigm of early dissemination implies that disseminated cancer cells remain dormant or under control for prolonged periods of time, often for decades, before developing into overt metastases. It is not yet clear why only some disseminated cancer cells develop into metastases and why not all patients with disseminated cancer cells develop metastatic disease. Tumour-initiating cells may only represent a small fraction of disseminated cancer cells, as proposed by the cancer stem cell hypothesis. Alternatively, disseminated cancer cells may require additional adaptation to their new environment or specific signals delivered by their new environment to exit from dormancy (the metastatic niche model). It is certain that the immune system plays a crucial role in controlling the dormancy of disseminated cancer cells, since both acquired and iatrogenic immune

suppression accelerates the development of metastases. A better understanding of the immune mechanisms keeping disseminated melanoma cells in a state of dormancy could lead to the development of interventions to help to slow down cancer progression, improve the treatment of advanced melanomas and increase patient survival. In this regard, immunotherapies such as cancer vaccines or anti-CTLA4 monoclonal antibodies (which prevent T lymphocyte anergy) are likely to be most successful if used to delay the onset of metastasis in patients with dormant disseminated cancer cells and minimal disease.

In this chapter, we will review our current understanding of the metastatic process and discuss possible therapeutic implications. We will address some of the key questions arising from recent data, and their relevance to the treatment of patients. For example, if metastases derive from cancer cells that have already disseminated at the time of diagnosis, how do the size of the primary tumour and the extent of lymph node invasion still predict survival? Are there any features of the primary tumour that correlate with early dissemination, or does the primary tumour itself contribute to the growth of disseminated cancer cells? And how do the answers to these questions impact on our ability to understand which individuals will develop metastatic disease and how to best manage patients for maximum survival benefit?

2. The process of metastasis

Metastasis is a multistep process in which cancer cells derived from the primary tumour migrate to regional or distant sites where they reinitiate their development (Chiang and Massague, 2008). Cancer cells can disseminate directly through the blood or may enter the circulatory system via the lymphatics (Wong and Hynes, 2006). While tumour cells are reliant on the blood for their dissemination, the circulatory system is essentially a hostile environment; intravenously injected cancer cells are cleared after just a few days. To successfully use the blood circulation to colonize a new site, cancer cells must enter the vessel, brave the substantial shear forces of the blood flow and then arrest their movement in order to extravasate and invade the tissue. Lymph may be gentler to disseminated cancer cells, in part because shearing forces there are lower, but lymph nodes may serve as filters. Each type of cancer exhibits a preferred metastatic profile. For example ocular melanomas typically metastasize to the liver; cutaneous melanomas prefer the skin, lungs, liver, bones and brain; while prostate cancers often spread to the bones, liver, brain and lung (Weinberg, 2007). The reasons underlying such preferences for different metastatic sites are important to understand. In some cases the sites where circulating cancer cells stop may be determined by physical restrictions imposed by the vasculature. For example, large cancer cells might be more likely to be arrested in small lung capillaries. Alternatively, chemokines may be exploited by tumour cells in order to actively target specific organs; breast cancer cells expressing CXCR4 are preferentially attracted to organs expressing the CXCR4 ligand CXCL12 (Helbig et al., 2003; Muller et al., 2001). Similarly, expression of CCR7 by B16 melanoma cells increases their homing to lymph nodes and the outgrowth of lymph node metastases (Wiley et al., 2001). However, homing is only a small part of determining the eventual pattern of metastasis, as the ability of the cancer cells to survive and proliferate in their ectopic location is a key factor. This is evidenced by the fact that less than 0.01% of circulating cancer cells will successfully develop into metastases (Chambers et al., 2002; Luzzi et al., 1998). As originally hypothesized in 1889 by Paget, circulating cancer cells will only develop into overt metastasis if they encounter a favourable environment (Paget, 1989).

This has been clearly demonstrated in the RETAAD model of melanoma. RETAAD mice are transgenic for the human RET oncogene, which is specifically expressed in melanocytes. These fully immune-competent mice develop spontaneous uveal melanoma. While cancer cells derived from the primary eye tumor disseminate to all tested organs and tissues, metastases develop almost exclusively in the skin, muscles, lungs and reproductive tract (Eyles et al., 2010).

3. Initial routes of dissemination

Cancer cells disseminate through the blood and the lymph, although it can be challenging to discern which route is preferred by different tumours. Cutaneous melanomas were thought to disseminate mainly through the lymph, but some visceral metastases occur without lymph node invasion. In addition, it had been claimed that ocular melanoma disseminates exclusively through the blood (Clarijs et al., 2001), however, data from both humans and mice now indicate dissemination via the lymph as well (Boonman et al., 2004; Harris et al., 2007). Tumour growth itself is associated with profound alterations of the blood and lymph vessels that may be advantageous to disseminating cells. The growth of a tumour requires the development of new blood vessels in and around the lesion. These newly-generated vessels convey nutrients and oxygen to the growing tumour, but are also used by cancer cells to escape the primary tumour and disseminate. The relatively high leakiness of tumour-associated blood vessels may also facilitate cancer cell intravasation. Similarly, tumour growth is associated with lymphangiogenesis (the growth of lymphatic vessels) both within and around the tumour and in the tumour-draining lymph node. Using the RETAAD model of spontaneous melanoma, we found that the growth of lymphatic vessels precedes melanoma cell migration to the draining lymph node and correlates with the size of the primary tumour. This suggests that the primary tumour secretes factors which favour lymphangiogenesis in the draining lymph node. Tumour tissues are also chronically inflamed, and inflammation encourages both angiogenesis and lymphangiogenesis. This may, at least in part, contribute to the well-established link between tumour inflammation and cancer progression. It is therefore reasonable to consider that melanomas can disseminate through the lymph or through the blood and that the actual route of dissemination may vary according to local conditions.

4. Early cancer cell dissemination

Until recently, cancer cell dissemination was thought to be a late event in disease progression (Fearon and Vogelstein, 1990; Fidler and Hart, 1982; Fidler and Kripke, 1977). Metastasis was believed to occur once the primary tumour had reached a certain size. Indeed the risk of metastatic disease increases with the size of the primary tumour. The recent advent of sensitive and reliable techniques to detect circulating tumour cells has revealed that tumour cells can in fact disseminate long before the primary tumour reaches a clinically detectable size (Pantel and Brakenhoff, 2004; Wharton et al., 1999). In the RETAAD model, melanoma cells can be detected in all tissues and organs by the time mice are two weeks of age, while the primary tumour is only visible after 5 to 8 weeks. In human uveal melanoma, calculation of tumour doubling times also suggests that metastases derive from tumour cells that disseminate on average three years before the primary tumour is

diagnosed (Eskelin et al., 2000). Moreover, at the time of dissemination, the size of the primary tumour represents less than 1% of its final size at the time of diagnosis. Even though 98% of patients are free of metastasis at the time of surgery, about 50% of them will eventually succumb to metastatic disease (Eskelin et al., 2000). Similar conclusions have been reached in other types of cancer. For example, whole exome sequencing of pancreatic tumours has confirmed that metastases derive from cells that disseminate roughly three years before diagnosis (Luebeck, 2010). Strikingly, Vinokurava et al. reported five cases of patients with non-invasive cervical intraepithelial neoplasia (CIN) who relapsed 4 to 12 years after radical hysterectomy. Cervical tumours are caused by random integration of the human papilloma virus (HPV) genome, and mapping the site of HPV integration confirmed a common clonal origin of the primary lesions (CIN) and metachronous metastases (Vinokurova et al., 2005). Remarkably this implies that transformed cells can even spread from pre-invasive cervical lesions, and go on to cause clinical disease. In summary, a growing body of convergent findings in both mice and humans shows that tumour cell dissemination can be an early event in cancer progression and sometimes occurs even before the primary tumour is diagnosed.

5. What drives cancer cell dissemination?

Cancer cells within the primary tumour compete with each other for space and nutrients. The evolution of cancer cells is therefore likely to be affected by this competition, and selection should favour cancer cells with advantageous characteristics (Gatenby and Gillies, 2008). What could be the selective pressure responsible for the early acquisition of a motile phenotype by the cancer cells in the primary tumour? If disseminated cancer cells remain dormant for prolonged periods of time, metastasis is unlikely to be positively selected: selection is blind to the future. Perhaps unexpectedly, hints may come from the analysis of tumour shapes. Primary tumours often display a multinodular, papilloma-like structure. The shape of the primary tumour correlates with the risk of disease progression (Goutzanis et al., 2008; Tambasco and Magliocco, 2008) and is therefore linked to metastatic propensity. *In silico* modelling suggests that tumour multinodularity results from the competition among cancer cells for nutrients (Ferreira et al., 2002; Mallet and De Pillis, 2006). This competition is particularly keen in non-vascularised tumours. We showed that such multinodular growth is determined by intercellular adhesion, adhesion between cells and the extra-cellular matrix and cancer cell motility (Narang, 2011). Importantly, these *in silico* models show that under nutrient-limited conditions, tumour growth is faster if it is multinodular. Therefore, acquisition of a metastatic phenotype could be selected because it favours the growth of the primary tumour (Norton, 2005); dissemination would be more of an accidental by-product resulting from the acquisition of cellular behaviours aimed at benefitting the primary tumour. This would explain why the risk of metastasis correlates with primary tumour size.

6. Cancer cell dissemination and mesenchymal transition

In order to disseminate, cancer cells need to detach from the primary tumour and become motile. Cancer cells must therefore decrease expression of various adhesion molecules such as cadherins and catenins, increase expression of proteases (e.g. matrix metalloproteinases

or MMP) able to degrade the extracellular matrix, and enhance their motility. So how do cancer cells simultaneously acquire this panel of phenotypic changes? Epithelial to Mesenchymal transition (EMT) is often considered the first step of cancer cell progression toward metastasis. The term EMT traditionally refers to the formation of mesenchymal cells (loosely adherent, often motile cells embedded in the extracellular matrix) from a primitive epithelium during embryonic development (Thiery, 2002). The process of EMT is associated with down-regulation of cell surface molecules involved in intercellular contacts and up-regulation of mesenchymal markers (vimentin, N-cadherin). Similar changes are indeed observed during carcinoma progression. It is therefore likely that the mechanism by which sessile carcinoma cells become motile resembles EMT. Even though melanocytes are not of epithelial origin, expression of mesenchymal markers correlates with tumour aggressiveness and propensity to metastasize.

Melanocytes and melanocyte stem cells derive from melanoblasts, a non-pigmented cell population which migrates from the neural crest during embryonic development (Thomas and Erickson, 2008). Therefore, acquisition of a motile phenotype by melanoma cells only requires re-expression of a previously silenced pathway. Weinberg and coll. have shown that ectopic expression of just a few genes in human melanocytes was sufficient to make them tumourigenic and highly metastatic (Gupta et al., 2005). The same set of genes transferred into fibroblasts or epithelial cells resulted in only localized tumour formation. Therefore, cells of melanocytic origin are more prone to undergo mesenchymal transition, and lineage-specific factors contribute to the tendency of melanoma to metastasize.

7. Clinical relevance

If cancer cell dissemination can occur early on during disease development, it is likely that many patients already have cancer cells disseminated throughout their body at diagnosis. A recent meta-analysis including 38,918 patients with cutaneous melanoma showed that patients whose primary tumour had a Breslow's thickness above 1 mm, was ulcerated and/or had a mitotic index above 1 mitose /mm² were at higher risk of melanoma-related death, even in the absence of invaded nodes and metastasis (Balch et al., 2009). Because metastases have a long latency period, it has been hypothesized that these early disseminating cancer cells were unable to develop into metastases, supporting the traditional notion that the spread of cells causing metastases occurred late during disease. Accordingly, accumulation of additional genetic changes would be required for the development of full-blown metastatic potential. However, recent studies in mouse models of breast cancer and melanoma have shown that early disseminating cancer cells are fully competent to develop into metastases (Eyles et al., 2010; Husemann et al., 2008). Moreover, genetic comparison of primary human tumours, disseminated cancer cells and metastases confirmed that metastases do derive from early disseminating cancer cells (Klein, 2009). The interesting question of the factors controlling this long-term latency of early disseminated tumour cells is then raised. The immune system is likely to play a major role, but if so, does the treatment of the primary tumour impact disease progression and is there really any benefit from removing the tumour-draining lymph node? More than 30 years ago, B. Fisher predicted that if cancer (in this case, breast cancer) were a systemic disease from its inception, the extent of local treatment should not affect patient survival (Fisher, 1980). Several of his predictions also hold true for melanoma, in particular for primary tumours presenting with pejorative prognostic factors.

8. Tumour excision

It has been known for more than 50 years that melanoma cells often disseminate locally (up to 5 cm away) around the primary tumour. Initially it seemed logical to excise these distant cells by using a large enough surgical margin. A first randomised prospective trial was conducted in the 1970's to determine whether there was any significant clinical benefit associated with a 5 cm margin excision compared to a 2 cm margin (Wargo and Tanabe, 2009). No statistically significant difference was observed in distant metastases or overall survival. This conclusion was counter-intuitive and difficult to accept, and so at least four other prospective randomized studies were conducted between 1980 and 2000 to determine the optimal margin of excision for cutaneous melanomas (Balch et al., 2001; Balch et al., 1993; Cohn-Cedermark et al., 2000; Ringborg et al., 1996; Thomas et al., 2004; Veronesi and Cascinelli, 1991; Veronesi et al., 1988). These trials compared various margins from 1 to 5 cm, in melanomas of different thickness and in a total of 2,861 patients. None of these trials found any survival benefit associated with the larger excision. Similarly, the survival of patients with anal melanoma is not different whether they are treated by local tumour excision or rectal resection (Kiran et al., 2010). Regardless, the consensus in clinical practice is to use large margins to excise thick primary tumours.

Besides their obvious implications for melanoma management, these observations lead to important theoretical conclusions. There is no doubt that some cancer cells are left behind after a narrow excision of the primary tumour, but the patient is able to control these cancer cells to the extent that they do not affect patient survival. Alternatively, these cells may not play a major role in the development of the distant metastases that cause patient death because metastases develop from cancer cells that have already disseminated at the time of surgery, and not from residual cancer cells left in the vicinity of the primary tumour. But since surgery cures most early stage patients, one has to conclude that only some primary tumours have the properties that favour metastases, and that most patients are able to control the disseminated cancer cells. A systemic biological process, for example the immune system, is therefore able to prevent the proliferation of cancer cells, provided they are not too numerous.

9. Sentinel lymph node biopsy

Infiltration of melanoma cells in the tumour-draining lymph node has also been extensively studied. The results of sentinel lymph node biopsy followed by examination using H&E stains and immunohistochemistry is one of the most reliable predictors of patient survival. However, it is now recognized that not all tumour-draining lymph nodes containing disseminated cancer cells will progress into palpable metastases. The number and localisation of the disseminated cancer cells within the lymph node seem to be important. In one study, 50% of patients with thin primary tumours had tumour-draining lymph nodes containing melanoma cells, as judged by RT-PCR, but 85% of them survived more than 5 years (Shivers et al., 1998). In addition, the melanoma-specific survival of patients with subcapsular deposits less than 1 mm in diameter is the same as that of patients with negative lymph nodes (Starz et al., 2004). However it is not clear whether these few cells are fully-fledged melanoma cells or whether they represent sub-capsular nevi. In any case, the patient's own immune system is probably able to cope with a limited number of cancer cells disseminated in the draining lymph node. One could even argue that the presence of cancer

cells in the draining lymph node might facilitate the induction of an anti-melanoma immune response (Ochsenbein et al., 2001). Using various mouse tumour models, including the B16 melanoma model, these authors suggested that tumour-specific induction of protective cytotoxic T cells (CTLs) could depend on sufficient tumour cells reaching secondary lymphatic organs. However, whether this finding holds for human tumours is unclear.

For almost 20 years, patients with intermediate or thick primary melanomas (Breslow's depth above 1 mm) have been advised to undergo sentinel lymph node biopsy (SLNBx) and this procedure has become a standard approach (Wargo and Tanabe, 2009). When metastatic cells are identified in the sentinel lymph node, a complete regional lymph node dissection (CRLND) is performed. Indeed, the result of SLNBx and CRLND accurately predicts patient survival. The 5-year survival of patients with positive SLNBx (72.3%) is significantly shorter than that of patients with negative SLNBx (90.2%; $p < 0.001$) (Baldwin et al., 2010). In addition, the efficacy of adoptive immune therapy depends on the number of metastatic lymph nodes (Khammari et al., 2007). Patients presenting with a single metastatic lymph node benefit from adoptive treatment with tumour-infiltrating lymphocytes (prolonged overall survival $p = 0.0125$; decreased relapse rate $p = 0.022$), but not those with more than one invaded node. However, four controlled studies have shown that there is no survival benefit associated with early removal of non-palpable lymph nodes (Balch et al., 2000; Cascinelli et al., 1998; Sim et al., 1986; Veronesi et al., 1982; Zitelli, 2008). The prospective randomized Multi-centre Selective Lymphadenectomy Trial (MSLT-1), conducted between 1994 and 2002 with 1269 patients, clearly confirmed that there is no survival benefit for patients undergoing wide excision and SLNBx with immediate CRLND if nodal micrometastases were detected compared to those undergoing wide excision and postoperative observation of regional lymph nodes with therapeutic lymph node dissection (lymphadenectomy) if nodal relapse occurred (Baldwin et al., 2010; Morton et al., 2006). The Sunbelt Melanoma trial analysed the survival of patients with minimal infiltration of the sentinel lymph node by melanoma cells. Patients whose SLNBx was negative by standard immunopathology/immunochemistry methods, but positive by RT-PCR, were randomized to observation or CRLND treatment; but interestingly, no difference in overall survival was found between the two groups (McMasters et al., 2001). In conclusion, while lymph node invasion correlates with shorter survival, early removal of non-palpable lymph nodes containing micrometastases does not improve survival. It is still unknown whether removal of palpable metastatic lymph nodes improves survival, but this question is being addressed by the MSLT-II trial.

Similar conclusions have been reached in studies on other types of cancer. For example, Sleeman et al. analysed 7 randomized clinical studies, totalling 3,351 patients with breast cancer (Sleeman et al., 2011). None of these studies showed any overall survival or disease-free survival benefit from removing tumour-draining lymph nodes. A recent report also compared 891 breast cancer patients with metastasis-containing sentinel lymph nodes undergoing either sentinel lymph node dissection alone or complete axillary lymph node dissection (Giuliano et al., 2011). Five years after surgery, no significant difference in the rates of overall survival (91.8% vs 92.5%) or disease-free survival (82.2% vs 83.9%) was observed. In the same indication, Bidart et al. found that 82% of patients with tumour cells in the bone marrow do not relapse at least for the 6 years of the study (Bidard et al., 2008). Veronesi et al. performed a meta-analysis with an average follow up of 30 years. While the presence of tumour cells in the internal lymph nodes was a strong predictor of patient

survival, extensive lymphadenectomy did not change survival (Veronesi et al., 1999). Collectively, these observations confirm that patients are able to control disseminated cancer cells for prolonged period of times, provided they are not too numerous.

10. Reasons to remove the tumour-draining lymph nodes

Despite the lack of clinical evidence supporting a benefit of extensive lymph node dissection, there are theoretical reasons to believe that removal of invaded draining lymph nodes may be beneficial. Firstly, cancer cells secrete factors that facilitate metastasis. Cytokines such as TGF- β , which is abundantly secreted by tumours can suppress the anti-tumour immune response. Tumours also secrete GM-CSF which plays a crucial role in the accumulation of myeloid-derived suppressor cells (MDSC). We found that tumours in RETAAD mice also secrete chemokines that attract MDSC. MDSC favour tumour cell proliferation, metastasis, and dampen the immune response. In melanoma patients, regulatory T cells, which suppress the immune response, are twice as frequent in metastatic lymph nodes as in tumour-free nodes (Viguier et al., 2004). Primary tumours also secrete growth factors that directly stimulate the proliferation of disseminated cancer cells or micrometastases. Tumour supernatants have also been involved in the development of the cellular clusters of non-tumoural cells that facilitate organ colonization by the cancer cells. These clusters have been referred to as pre-metastatic niches (Kaplan et al., 2005). In summary, large tumour masses participate in immunosuppression to favour tumour growth, and some studies show that surgery to remove such masses could improve the functionality of the anti-tumour response (Tatsumi et al., 2002). It is therefore difficult to argue against the removal of any detectable tumour cell.

11. Reasons not to remove tumour-draining lymph nodes

There are also theoretical reasons explaining why lymph node removal does not improve survival, or could even be deleterious. Surgery may sometimes result in the spread of cancer cells into the circulation, as has been shown in colorectal and prostate cancers (Yamaguchi et al., 2000). This has also been reported for cutaneous and uveal melanoma (De Giorgi et al., 2010). Surgery also induces inflammation, and the link between inflammation and cancer progression is well established. Wound healing is known to induce local production of TGF β and bFGF, which promotes the growth of B16 tumours in experimental models (Hofer et al., 1998). Similarly, trauma facilitates the implantation of mammary carcinoma cells (Murthy et al., 1989). Alteration of the lymphatic drainage may further worsen these effects. Lymph node removal reduces fluid drainage and favours oedema development which may also cause increased inflammation. While inflammation stimulates lymphangiogenesis (Angeli and Randolph, 2006), inhibitors of lymphangiogenesis have been shown to increase local inflammation. Conversely, stimulation of lymphangiogenesis reduces chronic skin inflammation (Huggenberger et al., 2010). All these studies are consistent with the idea that inefficient drainage increases inflammation. Inflammation induced by extensive surgery could then favour angiogenesis and suppress the anti-tumour immune response. Since suppression of angiogenesis (Holmgren et al., 1995; Naumov et al., 2006) and the immune response (Eyles et al., 2010) are considered the main mechanisms controlling dormancy of disseminated cancer cells, this would explain how surgery can influence the outgrowth of distant micrometastases.

In fact, there is substantial evidence, especially in colorectal cancer, that surgery contributes to metastasis (van der Bij et al., 2009). In melanoma patients, similar observations have been reported. Tseng et al noted the cases of two patients with giant upper extremity melanomas and no sign of progression for years. However, six months after surgery, both patients developed extensive metastatic disease (Tseng et al., 2009). Using the RETAAD model of uveal melanoma, we found that early removal of the primary eye tumour does not always reduce metastasis. In a few instances, incomplete enucleation was followed by rapid local recurrence, accelerated tumour growth and increased dissemination. Similarly, removal of the mandibular lymph node which drains the primary eye tumour resulted in increased angiogenesis and accelerated melanoma cell dissemination in this model. Taken together, these observations indicate that surgery aimed at removing the primary tumour and cancer cells disseminated locally could stimulate the growth of distant metastases. To address this issue and the considerable morbidity associated with CRLND, Murali et al. recently established a set of clinical and histo-pathological features predicting the negativity of non-sentinel lymph nodes (Murali et al., 2010). Murali et al. recommend low risk patients to be spared unnecessary surgery.

12. Immune surveillance and immune control of disseminated cancer cells

The immune surveillance theory originally proposed by L. Thomas (Thomas, 1959) and F. Burnet (Burnet, 1970) in the 50's proposes that the immune system plays a critical role in preventing cancer development and progression. This idea was initially broadly accepted, and then almost universally rejected, until the last decade when R. Schreiber, M. Smyth and their colleagues conclusively showed that the immune system controls not only the incidence of specific cancers in mice, but also interacts in a complex way with the tumour to shape its immune profile (Dunn et al., 2004). It is now recognized that both immunodeficient animals (Swann and Smyth, 2007) and patients under immunosuppression (Peto, 2001) have a higher incidence of cancer. The immune system is not only important to eliminate subclinical primary tumours. It plays a crucial role in controlling the dormancy of disseminated cancer cells, since immune suppression also accelerates the development of metastases. While pregnancy does not increase the risk of melanoma (Lens and Bataille, 2008), it may accelerate the development of metastatic disease (Sato et al., 2008; Youn et al., 2010). We also showed that RETAAD mice depleted of CD8⁺ T cells develop visceral metastases much earlier than control mice (Eyles et al., 2010; Lengagne et al., 2008). Pathological examination of the lungs of CD8-depleted animals revealed a higher density of proliferating cancer cells. This suggests that CD8⁺ T cells control metastatic dormancy through their anti-proliferative activity (for example by secreting cytostatic cytokines) rather than by direct cytotoxicity. Striking evidence for a role of the immune system in controlling disseminated cancer cells in humans comes from iatrogenic cases of allogeneic melanoma after organ transplantation (Penn, 1996). MacKie et al. reported two cases of such melanoma developing in patients grafted with the kidneys of a donor who had been treated for superficial melanoma without any detectable metastases 16 years before the transplantation (MacKie et al., 2003). Some disseminated melanoma cells apparently survived in the donor for this long period of time and escaped from dormancy only after transplantation into the immune-suppressed recipients. Tumour cells can escape immune control through a variety of mechanisms (Mapara and Sykes, 2004; Zou, 2005). In fact, the development of metastases in cancer patients with active anti-tumour immune responses is one of the most disturbing

paradoxes of cancer immunology. Indeed, in most cancer patients, anti-tumour T cell responses can be detected. For the first time in 2010, the US Food and Drug Administration approved a therapeutic cancer vaccine, Provenge, to treat asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer (Kantoff et al., 2010). While significant progress has been made in increasing the strength and quality of the immune response induced by candidate cancer vaccines, clinical benefits are still limited (Rosenberg et al., 2004). Cancer vaccines have most frequently been tested in advanced cancer patients with bulky tumours. Work in preclinical models however, suggests that such vaccines may be more efficient at controlling the dormancy of disseminated cancer cells.

13. Conclusion

Most patients with early stage melanoma are cured by local surgery. However, extensive surgical treatment of more advanced patients may not always be beneficial because some primary tumour cells have the capacity to disseminate early during disease progression. Distant metastases may not develop from nodal metastases detected at diagnosis but rather from cancer cells already disseminated throughout the body. Once the main tumoural mass has been removed, the immune system of the patient should be able to cope with the residual cancer cells. In these patients, extensive surgery may even accelerate the outgrowth of distant metastases by adversely affecting the immune response and favouring the escape of disseminated cancer cells from dormancy. Collectively, the data presented in this review plead for a limited surgery of the primary tumour combined with systemic adjuvant therapy.

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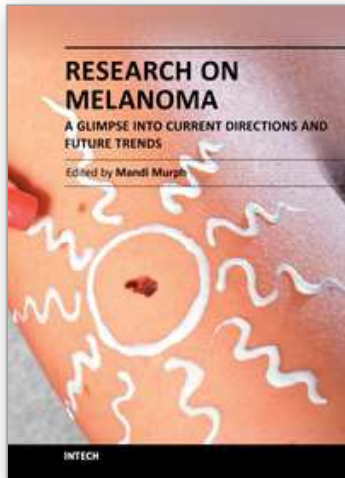
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The book *Research on Melanoma: A Glimpse into Current Directions and Future Trends*, is divided into sections to represent the most cutting-edge topics in melanoma from around the world. The emerging epigenetics of disease, novel therapeutics under development and the molecular signaling aberrations are explained in detail. Since there are a number of areas in which unknowns exist surrounding the complex development of melanoma and its response to therapy, this book illuminates and comprehensively discusses such aspects. It is relevant for teaching the novice researcher who wants to initiate projects in melanoma and the more senior researcher seeking to polish their existing knowledge in this area. Many chapters include visuals and illustrations designed to easily guide the reader through the ideas presented.

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