

# Chapter 7

## Tumor-Derived Factors Responsible for Dendritic Cell Dysfunction

Alberto Pinzon-Charry and J. Alejandro López

**Abstract** Perpetuation of immune deficiency throughout tumor development is, to a great degree, the result of impairment of dendritic cell function by products secreted by tumors. They include cytokines, non-tumor-specific molecules (gangliosides, prostanoids, nitric oxide, etc.) and tumor-(specific) antigens (MUC-1, PSA, Her-2 neu). They may engender a distortion of dendritic cell development, block dendritic cell maturation, induce dendritic cell apoptosis or interfere with antigen presentation. Identifying those molecules and their interaction with dendritic cells will accelerate the development of more efficient immunotherapies. In this chapter we review the current literature on these interactions and highlight the possible avenues of minimization of their deleterious effects.

### 7.1 Introduction

The induction of an effective immunological response against tumors is mainly dependent on the effector cells of the innate and adaptive immunity with DC playing a very important regulatory role. Therefore, the context in which tumor antigens are presented to the immune system dictates the efficacy of tumoricidal responses. The spontaneous remission observed in a number of human cancers suggests that the immune system has the potential to present antigens adequately and thus eliminate malignant cells (Bodey 2002). However, tumors usually evade immune clearance due to a number of mechanisms including recruitment of regulatory cell types (Pekarek et al. 1995; Vence et al. 2007), deletion of effector cells (Staveley-O'Carroll et al. 1998; Saito et al. 2000) or secretion of immunosuppressive factors (Gabrilovich 2004). Here, we examine evidence on the role of tumor-derived factors inducing DC dysfunction and particularly the alteration of DC differentiation, maturation and longevity as a mechanism for immune suppression.

A. Pinzon-Charry (✉)  
Bancroft Centre, L floor, Queensland Institute of Medical Research, Brisbane,  
QLD 4006, Australia  
e-mail: AlbertoP@qimr.edu.au

## 46 7.2 Cytokines and Growth Factors Affecting Dendritic 47 Cell Differentiation 48

49 One of the first cytokines reported to have an inhibitory effect on DC function  
50 in cancer was IL-10. This is a suppressive cytokine which exerts primarily anti-  
51 inflammatory functions and antagonizes several functions of antigen-presenting  
52 cells (APC), including DC. It has been shown to inhibit the ability of DC to  
53 stimulate T cells, inducing antigen-specific anergy (Steinbrink et al. 1999). IL-10  
54 release has been reported from tumors like melanoma, multiple myeloma and  
55 lung cancer (Kruger-Krasagakes et al. 1994; Smith et al. 1994; Gu et al. 1996) as  
56 well as tumor-infiltrating macrophages, lymphocytes and peripheral blood  
57 lymphocytes (Kim et al. 1995; Asselin-Paturel et al. 1998). Importantly, IL-10  
58 has been shown to prevent the differentiation of monocytes to DC (Allavena  
59 et al. 1998) as well as inhibit the antigen-presenting function of DC (Enk et al.  
60 1993; Buelens et al. 1997). In addition, increased serum levels of IL-10 correlate  
61 with numerical deficiency and immature phenotype of circulating DC subsets in  
62 patients with hepatocellular carcinoma (Beckebaum et al. 2004), indicating a  
63 clear association between tumor-related production of IL-10 and defects in DC  
64 differentiation .  
65

66 Secretion of IL-6 and M-CSF from carcinoma cells has also been observed to  
67 inhibit the differentiation of DC from CD34<sup>+</sup> myeloid progenitors (Menetrier-  
68 Caux et al. 1998). The molecular mechanisms responsible for this effect involve  
69 the modulation of GM-CSF and M-CSF receptor expression by tumor-secreted  
70 IL-6 and M-CSF (Menetrier-Caux et al. 1998). In addition, high levels of IL-6  
71 have been correlated with poor prognosis in patients with multiple myeloma,  
72 renal cell carcinoma, melanoma and colorectal cancer (Blay et al. 1992; Deehan  
73 et al. 1994; Tartour et al. 1996; Ratta et al. 2002). Tumor overproduction of  
74 IL-6 has been demonstrated to inhibit the colony growth of DC progenitors  
75 (Ratta et al. 2002) and sera from bone marrow of multiple myeloma patients  
76 (containing high levels of IL-6) have been shown to inhibit the induction of fully  
77 functional DC (Hayashi et al. 2003). Another study has demonstrated that IL-6  
78 plays a crucial role in maintaining an immature phenotype on DC in vivo (Park  
79 et al. 2004), confirming the significant role of IL-6 in the inhibition of DC  
80 differentiation both in vitro and in vivo.

81 Granulocyte/monocyte-colony-stimulating factor (GM-CSF) has also been  
82 associated with tumor-induced dysfunction of myelopoiesis. Spontaneous pro-  
83 duction of GM-CSF has been reported for several types of human tumor cell  
84 lines (Bronte et al. 2000) and production of this cytokine has been associated  
85 with the ability of cancer cells to metastasize (Tsuchiya et al. 1988). Although  
86 cancer cells modified to produce GM-CSF elicit robust antitumor immune  
87 responses by recruiting DC, the aberrant secretion of GM-CSF by some tumors  
88 could be deleterious to the host immune response. In mice, chronic GM-CSF  
89 production by tumors has been reported to suppress tumor-specific CTL  
90 responses through the generation of a population of inhibitory immature

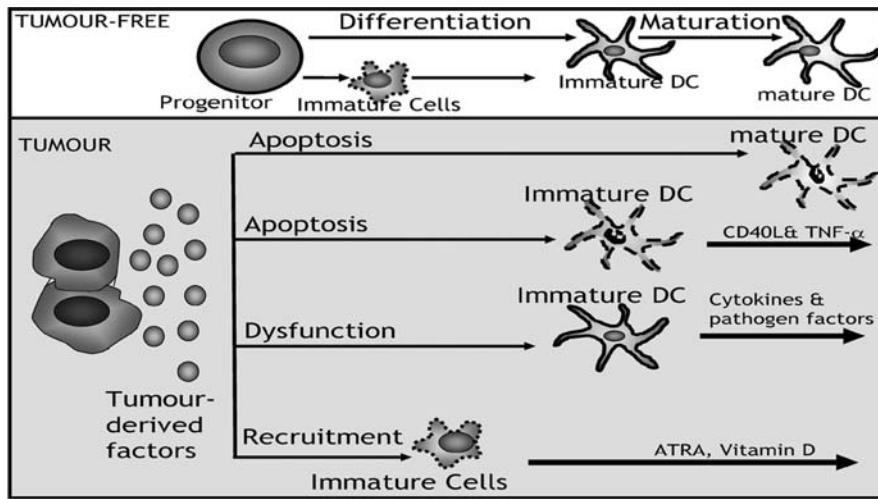
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91 APC. Although these immature cells could be generated by the administration  
 92 of GM-CSF alone, GM-CSF in combination with IL-4 induced their differ-  
 93 entiation into mature APC (Bronte et al. 1999) underscoring the necessity of an  
 94 appropriate cytokine milieu for adequate APC differentiation. Similarly, the  
 95 production of large amounts of GM-CSF by some tumors could impair the  
 96 immune response. This has been demonstrated in a study whereby vaccination  
 97 with tumor cells producing large quantities of GM-CSF resulted in substantial  
 98 accumulation of immature cells and immunosuppression in vivo (Serasini et al.  
 99 2004). The relevance of these findings in humans has been confirmed with  
 100 reports indicating that immune suppression and increased recurrence and  
 101 metastasis in patients with head and neck squamous cell carcinoma were  
 102 related to the presence of immature cells that secreted GM-CSF (Pak et al.  
 103 1995; Young et al. 1997). Interestingly, these cells could be differentiated into  
 104 fully functional DC in vitro, following culture with the pro-differentiating  
 105 factor 1 $\alpha$ ,25-dihydroxyvitamin D3 (Garrity et al. 1997).

106 VEGF is another tumor-derived factor shown to affect differentiation of  
 107 DC. VEGF is produced by different types of tumors and increased levels of this  
 108 cytokine have been associated with poor prognosis in cancer (Toi et al. 1996).  
 109 VEGF plays a role in inducing proliferation of endothelial cells and formation  
 110 of neo-vasculature within the tumor. It has also been demonstrated that VEGF  
 111 significantly affects the differentiation of multiple hematopoietic lineages in  
 112 vivo, including DC (Gabrilovich et al. 1998). The inhibitory effect of VEGF on  
 113 DC differentiation has been confirmed and increased VEGF levels have been  
 114 reported to correlate with reduced number of infiltrating and circulating DC in  
 115 patients with different types of cancer (Saito et al. 1998; Lissoni et al. 2001;  
 116 Takahashi et al. 2004). In addition to altered differentiation of DC, elevated  
 117 levels of VEGF have been associated with an increased number of immature  
 118 cells with immunosuppressive function in the circulation of patients with cancer  
 119 (Almand et al. 2000). Notably, these cells could be differentiated into mature  
 120 DC in vitro, after culture with all-*trans* retinoic acid (Almand et al. 2001).  
 121 More recently, inhibition of VEGF has shown to improve on DC maturation  
 122 while yielding discreet improvement on immune responses (Fricke et al. 2007).

### 123 124 125 7.3 Other Immune Mediators Affecting Dendritic 126 Cell Differentiation

127  
 128 Gangliosides (membrane-bound glycosphingolipids with a sialic acid moiety)  
 129 could contribute to tumor-induced immune suppression by altering differ-  
 130 entiation of several lineages and hematopoiesis (Sietsma et al. 1998)  
 131 (Fig. 7.1). A number of tumors including medulloblastoma, lymphoma,  
 132 melanoma, neuroblastoma, retinoblastoma and hepatoma are known to dis-  
 133 play an aberrant ganglioside composition (Birkle et al. 2003) also shedding  
 134 some of these molecules into the tumor milieu and the circulation (Ladisch  
 135



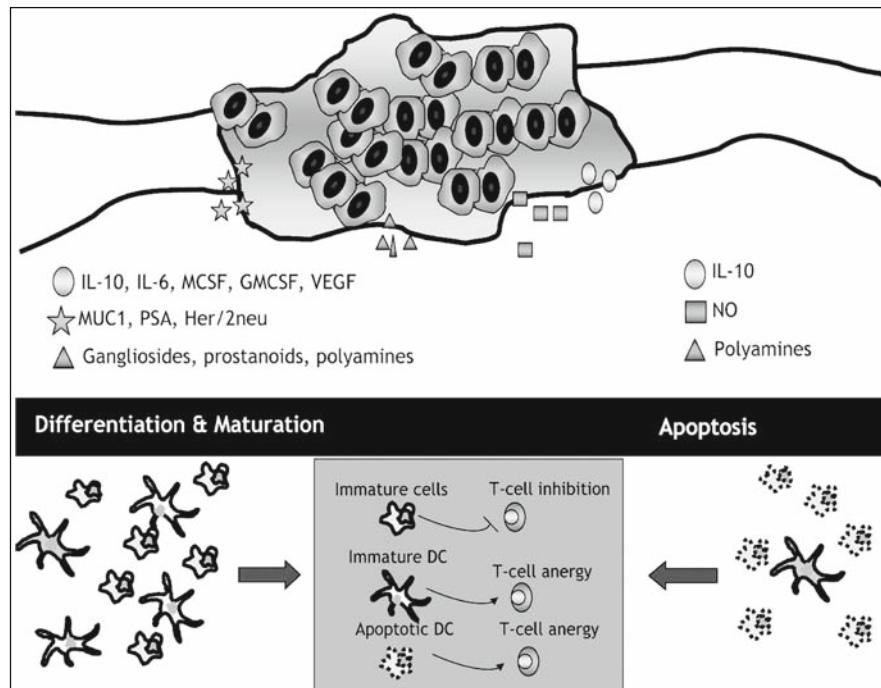
**Fig. 7.1 Mechanisms for tumor-induced dendritic cell dysfunction.** In a tumor-free environment (*upper panel*), hematopoietic precursors give rise to progenitors which differentiate into immature DC. Following antigen/'danger signal' encounter, immature DC undergo maturation and become specialized in antigen presentation. Under the influence of tumor-derived factors (*lower panel*), differentiation of DC is hampered resulting in the recruitment, accumulation and dysfunction of immature cells and immature DC. DC can also be induced to undergo apoptosis by tumor products. Immature cells can be differentiated into DC under the influence of factors like all-*trans* retinoic acid (ATRA) or vitamin D. Immature DC can be induced to mature with pro-inflammatory cytokines/pathogen-derived factors. Treatment of DC with TNF- $\alpha$  or CD40L confers protection to tumor-induced apoptosis promoting tumor clearance

et al. 1987; Portoukalian et al. 1993). More importantly, it has been shown that neuroblastoma and melanoma-derived gangliosides impair the phenotypic and functional differentiation of DC providing another mechanism for tumor-induced immunosuppression (Shurin et al. 2001; Peguet-Navarro et al. 2003) (Fig. 7.2). It appears that gangliosides interfere with the expression of costimulatory molecules and inhibit NF- $\kappa$ B (Caldwell et al. 2003). Interestingly, some DC function might be corrected with IL-15 (Tourkova et al. 2005).

There are other factors that could play redundant or synergistic roles on the inhibition of DC differentiation by tumors. Several reports now correlate alterations of arachidonic acid metabolism with carcinogenesis (Gately and Li 2004). Arachidonic acid metabolites (prostanoids) including prostaglandins and thromboxanes are synthesized by cyclooxygenase (COX)-1 and -2. In several types of cancer, including melanoma, colon, breast and lung carcinoma, alterations in the expression of these enzymes have been reported (Tsujii et al. 1997; Denkert et al. 2001). Most studies indicate that prostanoids have a role in tumorigenesis mostly through their pro-angiogenic effects (Gately and Li 2004).

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**Fig. 7.2 Tumor-induced dendritic cell dysfunction generates ineffective immune responses.** In the absence of tumor-derived factors, DC differentiate and mature appropriately. Mature DC increase their capacity to process antigens and express the cytokines and costimulatory molecules essential for initiating an effective immune response. Under the influence of tumor-derived factors, immature cells, immature DC and apoptotic DC are generated and accumulated. Although immature cells appear not to present antigens, they can suppress tumor-specific T-cell activation through the production of reactive oxygen species (ROS). Immature DC and apoptotic DC can present antigens but in the absence of adequate costimulation and cytokine secretion, they can induce anergy, abortive proliferation or induction of regulatory T cells, thus favouring tumor evasion

However, recent data indicate that prostanoids may also contribute to carcinogenesis through inhibition of DC differentiation. Indeed, it has recently been demonstrated that tumor COX-2 expression decreases host antitumor response by impairing DC maturation and activity (Sharma et al. 2003). This appears to be through specific signaling pathways. The EP2 receptor, one of the four receptors for prostaglandin E2 (PgE2), has been reported to mediate PgE2-induced inhibition of DC differentiation and function, playing an essential role in impaired antitumor responses (Yang et al. 2003). It has also been shown that COX-2-regulated prostanoids inhibit DC production of IL-12, increase secretion of IL-10 and contribute to tumor-induced inhibition of DC development (Sombroek et al. 2002).

## 226 7.4 Tumor Antigens and Metabolites Affecting Dendritic 227 Cell Differentiation

228  
229 Various reports indicate that other factors produced by malignant cells like  
230 tumor antigens (MUC1 and PSA) or polyamines (spermine) are also respon-  
231 sible for impaired DC maturation and function (Aalamian et al. 2003; Della  
232 Bella et al. 2003; Monti et al. 2004). Interestingly, it has been demonstrated that  
233 whereas DC readily take up tumor antigens from epithelial tumors such as  
234 MUC1 and HER-2/neu, these glycoproteins inhibit their own transport to late  
235 endosomal compartments for processing and binding to class II MHC mole-  
236 cules (Hiltbold et al. 2000).

237 Similarly, prostate-specific antigen (PSA) clearly inhibited the DC differen-  
238 tiation and maturation of DC in vitro (Aalamian et al. 2003). Although inhibi-  
239 tion of DC maturation by serum from prostate cancer patients correlate with  
240 PSA levels (Aalamian-Matheis et al. 2007), the physiological significance of  
241 these findings has not been proven *in vivo*. Polyamines, in contrast, appear to  
242 play a relevant role *in vivo*. Putrescine, spermidine and spermine are essential  
243 for mammalian cell proliferation and differentiation. They have been impli-  
244 cated in impaired DC maturation and, more importantly, a significant negative  
245 correlation has been found between plasma levels of spermine and DC produc-  
246 tion of IL-12 in patients with breast cancer (Della Bella et al. 2003). These  
247 molecules have also been implicated in the inhibition of T-cell activity by  
248 immature suppressive cells *in vivo* (Bronte et al. 2003). Given that polyamines  
249 are nutrients constantly produced in the tumor microenvironment, these mole-  
250 cules could assist tumor evasion by supporting tumor growth and affect DC  
251 differentiation and T-cell function. Similarly, a product of the cleavage of  
252 surface death receptor 6 (DR6) overexpressed in tumors has been described to  
253 interfere with DC development (Derosa et al. 2008).

## 254 255 7.5 Implications of Altered Dendritic Cell Differentiation

256 DC precursors and immature DC gain access to peripheral blood en route to  
257 peripheral tissues where they play an essential role in immune surveillance.  
258 However, the accumulation of immature cells associated with decreased num-  
259 ber of circulating DC (Young et al. 1997; Almand et al. 2000, 2001) has  
260 deleterious effects for tumor surveillance. In patients with head and neck  
261 carcinoma, immature cells play a role in suppression of T-cell responses to  
262 recall antigens (Pak et al. 1995) and elevated tumor infiltration with immature  
263 cells correlated with increased rate of recurrence and metastases (Young et al.  
264 1997). Immature cells have the capacity to inhibit MHC-I as well as MHC-II  
265 restricted T-cell responses (Almand et al. 2001). Although the mechanism of  
266 suppression has not been elucidated, a strict cell-to-cell contact with T cells is  
267 required to exert their suppressive activity (Almand et al. 2001). In mice,  
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immature cells obtained from tumor-bearing hosts have been reported to express higher levels of reactive oxygen species (ROS) and accumulation of H<sub>2</sub>O<sub>2</sub> and arginase activity appeared to contribute. Inhibition of ROS abrogated the inhibitory effect, indicating that immature cells suppressed T-cell responses via production of ROS (Kusmartsev et al. 2004). These data suggest that short-range immune mediators (i.e., ROS, H<sub>2</sub>O<sub>2</sub> or arginase) probably present lymphoid organs or at the tumor site on immature cells could play a crucial role in T-cell suppression.

Accumulation of immature cells displacing competent APC populations (i.e., DC) could also account for immune suppression. We have reported that in patients with solid tumors immature DC represent a significant proportion (up to 65%) of the circulating DC compartment, thus impairing immune activation (Pinzon-Charry et al. 2005). Interestingly and supporting a role for tumor products, a close correlation between accumulation of immature cells and tumor burden was evident. It is also tempting to speculate that while the systemic accumulation of immature cells could facilitate generalized immune dysfunction as a late event, immature APC present at the tumor site or lymphoid organs could play a role at an earlier phase in tumor progression. In fact, in patients with head and neck squamous cell carcinoma, tumor infiltration with immature cells has been correlated with increased rate of recurrence and metastases (Young et al. 1997)

Tumors may also interfere with DC maturation, the final differentiation step whereby DC specialized in antigen capture are transformed into DC specialized in stimulation of T cells. Immature DC fail to provide an appropriate costimulatory signal to T cells and tolerance or anergy may develop. Indeed, antigen presentation by immature DC has been reported to result in induction of tolerance through abortive proliferation or anergy of antigen-specific T cells *in vivo* (Probst et al. 2003). Immature DC can also induce tolerance through the generation of regulatory T cells that suppress immune responses by producing IL-10 and TGF- $\beta$  (Dhodapkar et al. 2001). Immature DC with deficient expression of costimulatory molecules and poor capacity to stimulate T-cell responses have been reported in patients with basal cell, colorectal and breast cancer (Chaux et al. 1996; Gabrilovich et al. 1997) and DC from melanoma patients have an immature phenotype, reduced T-cell stimulatory capacity and induce anergy in syngeneic CD4 $^{+}$  T cells *in vitro* (Enk et al. 1997).

DC-expressing indoleamine 2,3-dioxygenase (IDO) inhibit T-cell proliferation and promotes T-cell death as a result of prostaglandin induction (Braun et al. 2005). Notably, large numbers of IDO-expressing DC can be found in tumor-draining lymph nodes, suggesting that they may be involved in the immunological unresponsiveness seen in cancer patients (Munn et al. 2002). Therefore, it is tempting to speculate that similar mechanisms for induction of anergy occur *in vivo* at certain stages of tumor growth, an issue dealt in detail in a recent review (Munn and Mellor 2007).

## 316 7.6 Tumor-Derived Factors and Dendritic Cell Apoptosis

317  
 318 Additional studies revealing other mechanisms utilized by tumors to evade  
 319 effective immune responses have also been described. Induction of programmed  
 320 cell death impairing the function of the key elements of the immune response like  
 321 DC is one of such mechanisms. It has been demonstrated that DC underg

322  
 323  
 324 **Table 7.1** Tumor-derived factors responsible for DC dysfunction

325 Factor	Effect on DC	References
<b>Cytokines</b>		
327 IL-10	Impairment of differentiation, maturation and function in vitro and in vivo	Enk et al. (1993), Buelens et al. (1997), Allavena et al. (1998), Beckebaum et al. (2004)
330 IL-6	Increased apoptosis in vitro	Ludewig et al. (1996)
331	Impairment of differentiation and maturation in vitro and in vivo	Menetrier-Caux et al. (1998), Ratta et al. (2002), Hayashi et al. (2003), Park et al. (2004)
333 M-CSF	Inhibition of differentiation from CD34 <sup>+</sup> progenitors in vitro	Menetrier-Caux et al. (1998)
334 GM-CSF	Generation of immature APC with inhibitory role in vitro and in vivo	Pak et al. (1995), Garrity et al. (1997), Young et al. (1997), Bronte et al. (2000), Serafini et al. (2004)
337 VEGF	Alteration of differentiation of multiple lineages including DC in vitro and in vivo	Gabrilovich et al. (1998), Saito et al. (1998), Lissoni et al. (2001), Takahashi et al. (2004)
338	Accumulation of inhibitory immature cells in vitro and in vivo	Almand et al. (2000), Almand et al. (2001), Kusmartsev et al. (2004)
<b>Other mediators</b>		
343 Gangliosides	Impairment of phenotypic and functional differentiation in vitro	Shurin et al. (2001), Peguet-Navarro et al. (2003)
344	Phenotypic alteration and apoptosis in vitro	Kanto et al. (2001), Peguet-Navarro et al. (2003)
346 Prostanoids	Impairment of maturation and activity in vitro	Sombroek et al. (2002), Sharma et al. (2003), Yang et al. (2003)
348 Nitric oxide	Induction of apoptosis in vitro	Bonham et al. (1996)
349 Hyaluronan	Induction of apoptosis through induction of NO in vitro	Yang et al. (2002)
352 Polyamines	Induction of altered maturation in vitro	Della Bella et al. (2003)
354 DR6	Induction of apoptosis in vitro	Derosa et al. (2008)
<b>Tumor antigens</b>		
355 MUC1	Impairment of maturation and function in vitro	Hiltbold et al. (2000), Monti et al. (2004)
357 PSA	Alteration of differentiation and maturation in vitro	Aalamian et al. (2003)
359 Her/2neu		Hiltbold et al. (2000)

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361 apoptosis in vitro and in vivo after interacting with cancer cells or tumor-derived  
362 factors (Esche et al. 1999; Pirtskhalaishvili et al. 2000a,b; Balkir et al. 2004)  
363 confirming that malignancies use this mechanism to impair the generation of  
364 appropriate immune responses. Indeed, tumor cells are known to express or  
365 release numerous pro-apoptotic factors such as IL-10, nitric oxide, gangliosides  
366 or ceramides that induce DC to undergo apoptosis and may explain why T cells  
367 fail to become fully activated to eradicate adjacent tumor cells (Table 7.1).

AQ3 368 Apoptotic DC are ineffective at inducing immunity. It has been demon-  
369 strated that DC undergoing apoptosis deliver unusual activation during antigen  
370 presentation, leading to cellular unresponsiveness rather than effective immu-  
371 nity (Kitajima et al. 1996). Similarly, pre-apoptotic DC loaded with antigens  
372 show a marked decrease in their ability to induce antigen-specific immune  
373 responses in vivo (Colino et al. 2002). In breast cancer, significant apoptosis  
374 of blood DC has been reported (Pinzon-Charry et al. 2005). Circulating DC are  
375 essential for adequate immunity given that they continually replenish the pool  
376 of tissue-residing DC and play a critical role in shaping immune responses in  
377 vivo. Most circulating DC appear to be en route from the bone marrow to  
378 peripheral and lymphoid tissues or from non-lymphoid tissues to the regional  
379 lymph nodes and spleen (de la Rosa et al. 2003; Villadangos and Heath 2005).  
380 Given that apoptotic cells are rapidly cleared from the circulation, the observa-  
381 tion of a higher fraction of blood DC undergoing apoptosis in patients with  
382 breast cancer suggests increased turnover of these cells in vivo. Thus, continual  
383 efforts to replace the pool of blood DC from bone marrow would impose  
384 chronic stress on the immune system of breast cancer patients resulting in  
385 (i) relative paucity of DC in the circulation (Lissoni et al. 1999; Coventry  
386 et al. 2002) as well as (ii) failure to effectively replenish DC that infiltrate breast  
387 tumor tissue (Bell et al. 1999; Satthaporn et al. 2004) or (iii) migrate to lymphoid  
388 organs (Gabrilovich et al. 1997) for the initiation of T-cell immunity. Accord-  
389 ingly, in patients with operable breast carcinoma blood DC numbers are  
390 significantly reduced over prolonged periods of time suggesting diminished  
391 availability of DC precursors in cancer (Pinzon-Charry et al. 2007).

### 392 393 394 395 7.7 Concluding Remarks

396 Overall, the evidence presented here emphasize the importance of DC in the  
397 elicitation of effective antitumor responses as well as the tumor-induced DC  
398 defects as a mechanism to escape immune surveillance. Tumors have been  
399 demonstrated to release numerous immunosuppressive factors that exert  
400 systemic effects on immune cell function and in particular, affect DC. The result-  
401 ing dysfunction or apoptosis of mature DC, accumulation of immature DC or  
402 other immature cells with inhibitory functions would result in a significant defi-  
403 ciency in the induction of antitumor responses. The data examined also suggest  
404 that tumor-induced DC dysfunction represents one of the crucial mechanisms  
405 underlying tumor immune evasion and indicates that tumor-induced suppression

406 of DC has to be avoided if attempts to improve immune response in cancer are  
407 sought.

408 There is active interest in using DC and exploiting their distinctive immune  
409 functions as vectors for immune therapy of cancer. Nevertheless, given the  
410 heterogenous nature of DC dysfunction in cancer, multiple strategies would  
411 have to be considered. One approach could be the induction of differentiation  
412 or optimization of immature DC or immature cell function with differentiation  
413 agents or growth factors *in vivo* (Garrity et al. 1997; Almand et al. 2001).  
414 Another strategy would be the blockade of tumor-released factors that impair  
415 differentiation/function of DC *in vivo* (Gabrilovich et al. 1999). Finally, treat-  
416 ment of DC preparations (vaccines) with factors that increase their survival or  
417 resistance to apoptosis would be beneficial in the generation of antitumor  
418 immunity (Pinzon-Charry et al. 2006). Clear understanding of DC-related  
419 tumor evasion mechanisms will harness the potential utilization of DC as  
420 natural adjuvants in immunological therapy and assist the development of  
421 new methods to overcome the ineffective immunity against cancer (Lopez and  
422 Hart 2002).

423  
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**Chapter 7**

Query No.	Line No.	Query
AQ1	132	Please check the citation of Fig. 7.1.
AQ2	168	Please check the citation of Fig. 7.2.
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