Opposing Roles for IL-23 and IL-12 in Maintaining Occult Cancer in an Equilibrium State

Michele W. L. Teng1,2, Matthew D. Vesely3, Helene Duret1, Nicole McLaughlin1, Jennifer E. Towne4, Robert D. Schreiber3, and Mark J. Smyth1,2

Abstract
Cancer immunoediting, the process by which the immune system controls tumor growth and shapes tumor immunogenicity, consists of 3 stages: elimination, equilibrium, and escape. The molecular mechanisms that underlie the equilibrium phase, during which the immune system maintains tumor dormancy, remain incompletely defined. Here, we investigated the length of the equilibrium phase during immune control of methylcholanthrene (MCA)-induced or p53 mutant cancers and showed the critical and opposing roles of interleukin (IL)-23 and IL-12 in maintaining cancer cells in a state of immune-mediated dormancy. Inhibition of IL-23p19 was shown to reduce the malignant potential of lesions established by MCA inoculation, whereas inhibition of IL-12/23p40 enhanced tumor outgrowth. Furthermore, agonistic anti-CD40 antibody treatment mimicked the effects of anti-IL-23p19 monoclonal antibody treatment. Other cytokines such as IL-4, IL-17, TNF, and IFN-α, which are known to play important roles either in MCA tumorigenesis or in the elimination phase of cancer immunoediting, did not play critical roles in maintaining the equilibrium phase. Taken together, our findings show opposing roles for IL-23 and IL-12 in determining the outgrowth versus dormancy of occult neoplasia and suggest a potential long-term danger in using IL-12/23p40 antibodies for treating human autoimmune inflammatory disorders. Cancer Res; 72(16); 1–10. ©2012 AACR.

Introduction
Cancer immunoediting, the process whereby the immune system controls tumor outgrowth and shapes tumor immunogenicity, is comprised of 3 phases: elimination, equilibrium, and escape (reviewed in refs. 1, 2). The elimination phase involves the immune detection and destruction of tumor cells that have developed as a result of a failure of intrinsic tumor suppressor mechanisms. Elimination is a modernized view of the older concept of cancer immunosurveillance that now takes into account that efficient tumor destruction requires the coordinated effects of both innate and adaptive immunity. Sometimes not all tumor cells are eliminated and the residual tumor cells enter the equilibrium phase, in which the immune system and developing tumor enter into a temporary state of balance that controls tumor outgrowth. During equilibrium, tumor cells undergo editing as a consequence of genetic and epigenetic changes (such as DNA mutations or changes in gene expression) in the tumor cell population and a selective pressure exerted by adaptive immunity. Although this pressure is sufficient to control net tumor progression, eventually, if the immune response fails to completely eliminate the tumor, the process results in the selection of tumor cell variants that are able to resist, avoid, or suppress the antitumor immune response, leading to the escape phase and the outgrowth of clinically apparent cancers (3).

Although many immune components that participate in the equilibrium phase are known, the underlying mechanisms remain poorly defined. The presence of an equilibrium phase was suspected from earlier studies with experimental tumors (4–6), but only recently was experimentally shown using de novo carcinogen-induced tumors in mice (7). In that report, we showed the presence of equilibrium lesions following a low-dose regimen of the chemical carcinogen, methylcholanthrene (MCA), and showed that dormant cancer cells were present in these lesions together with actively proliferating immune infiltrates. Using depleting or blocking monoclonal antibodies (mAb), we further showed that equilibrium was maintained by components of adaptive immunity, namely CD4+ and CD8+ T cells, IFN-γ and IL-12p40 (7). In contrast, depletion of natural killer cells, blockade of NKG2D, or inhibition of TRAIL effector function failed to cause the emergence of progressively growing tumors (7). Since this initial demonstration of the existence of an equilibrium phase in 2007, 2 additional studies in mice showed that immunity controlled neoplastic disease for extended periods of time (8, 9). However, the questions...
remain whether additional immune components play a critical role in maintaining the equilibrium phase and whether there is a distinct function for interleukin (IL)-12 and IL-23, because these cytokines share the IL-12p40 subunit that was blocked in the previous report.

To address these questions we have since sought to (i) determine the length of time that immunity can manifest the equilibrium phase, (ii) determine the relative roles of 2 cytokines that contain the IL-12p40 subunit, that is, IL-23 and IL-12 in maintaining equilibrium, and (iii) assess the role of other cytokines and cell types known to regulate T-cell polarity in immune responses. The heterodimeric cytokine IL-23, which consists of the p40 and p19 subunits (as opposed to p40 and p35 forming IL-12), has emerged as a new player in promoting tumor growth and development (10, 11). Importantly, anti-IL-12/23p40 and anti-IL-23p19 antibodies are in early phase clinical trials in patients with psoriasis and inflammatory bowel syndromes (IBD; ref. 12, 13). The potential oncogenicity of each of these therapeutic approaches is of significant clinical importance given the chronicity of disease and elevated risk of malignancies in these patient groups (14, 15). Here, we show that the equilibrium phase can occur over extended periods of time and that both IL-23 and IL-12 maintain malignant cells in equilibrium with host immunity, but that IL-23 promotes cancer persistence whereas IL-12 prevents cancer outgrowth.

Materials and Methods

Mice

Inbred C57BL/6 wild-type (WT) mice were bred and maintained at the Peter MacCallum Cancer Centre (Peter Mac) as described previously (16). Mice 6 to 14 weeks old at the time of study initiation were used in all experiments. All experiments were carried out in accordance with guidelines set out by the Peter Mac Animal Experimental Ethics Committee.

Tumor models

Male WT mice were injected subcutaneously with low doses of MCA (Sigma Fine Chemicals) as described (7) and monitored for tumor development. At various time points after inoculation, MCA-treated mice bearing progressively growing primary fibrosarcomas were removed from the experiment (~10%–20% of group; stage I). The remaining mice in each group were then treated weekly with either clg or mAbs that deplete or block-specific immune components for 3 to 8 weeks (stage II). In most experiments (Figs. 2–6; Table 1), after a 1- to 3-week break after the last immune intervention treatment, mice then received either clg or anti-IFN-γ or a cocktail of anti-CD4/CD8/IFN-γ for a further 6 weeks (stage III). The timing and dose for each experiment are indicated in the figure legends. Mice were monitored for tumor development throughout for up to 600 days. Tumor size (cm²) for each individual mouse was recorded as described previously (7).

MAbs

The majority of the mAbs used for neutralization or depletion have been previously described (7). These include control lgs (PIP, a mAb specific for bacterial glutathione S-transferase), anti-CD8α (YTS169.4), anti-CD4 (GK1.5), and anti-IFN-γ (H22). These were produced from hybridoma supernatants and purified in endotoxin-free form by Protein G affinity chromatography (Leinco Technologies). Anti-AGP3 [control Ig (clg), 4D2], anti-IL-23p19 (16E5), and anti-IL-12/23p40 (C17.8) were provided by AMGEN and have been described previously (11). Anti-IL-10R (1B1.3) was produced in house and used as indicated. Anti-IL-17RA (M751) was also grafted on the same murine IgG1 background and kindly provided by AMGEN Inc. Anti-IL-10R (1B1.3), anti-IFNAR1 (MAR1-5A3), anti-IL-4 (11B11), and anti-TNF (TN3 19.12) were produced in house and used as indicated.

Statistical analysis

Significant differences in proportions of mice with tumor at each stage were determined by the Fishers Exact test. Values of P less than 0.05 were considered significant.

Results

The equilibrium phase is a protracted process

We previously described the presence of occult neoplastic lesions created by subcutaneous inoculation of low doses of the carcinogen, MCA (5–25 μg; ref. 7). Primary fibrosarcomas were shown to typically arise between 10 and 20 weeks after carcinogen inoculation, whereas the occult equilibrium lesions were dormant for up to 200 days before T-cell depletion and IFN-γ neutralization allowed escape from immune control (7). In the current study, we similarly found a low proportion of primary fibrosarcomas (4 of 20) and either tumor-free mice or those with stable masses (<0.5 cm²) that developed and disappeared over time (Fig. 1A). In addition, approximately 56% (8 of 15) of mice treated with a cocktail of anti-CD4/anti-CD8 and anti-IFN-γ for 8 weeks from day 200 after MCA inoculation developed fibrosarcomas, compared with only 1 of 16 treated with clg more than the same period (Fig. 1A and B). Similar results were found in female mice (Supplementary Fig. S1), confirming that equilibrium displays host sex independence. To investigate the latency period of equilibrium, we delayed conditional immune depletion for 300 (Fig. 1C and D) and 400 (Fig. 1E and F) days. Notably, immune depletion caused the outgrowth of fibrosarcomas (9 of 25 and 7 of 25, respectively), suggesting that significant numbers of mice still harbored occult malignant fibroblasts up to 400 days after MCA inoculation and long after stable lesions had macroscopically disappeared. These data revealed that immune-mediated dormancy of primary MCA sarcomas is a protracted process and that few equilibrium lesions spontaneously resolved (i.e., elimination) or escaped immune control over time.

To extend our findings to a spontaneous tumor model, we aged large cohorts of male and female C57BL/6 p53<sup>+/−</sup> mice for 750 days and monitored tumor development. We have previously shown that 45% to 60% of p53<sup>+/−</sup> mice develop tumors (predominantly sarcomas and lymphomas) by day 750 (17), and we observed similar findings in this study (47.5%–56.3% cohort, males mean age of death 616 ± 16 days, females...
534 ± 17 days; Supplementary Fig. S2A; ref. 18). Mice that were macroscopically tumor free at 750 days were then injected weekly for 8 weeks (days 750–799) with cIg or a cocktail of anti-CD4/-CD8/-IFN-γ antibodies. Over the next 200 days, a similar number of mice died in each group (Supplementary Fig. S2B), but the cohort of mice receiving a cocktail of anti-CD4/-CD8/-IFN-γ had a significantly higher proportion (6 of 25) of tumors develop (mostly low grade and large cell lymphoma) compared with the cohort of mice receiving cIg (1 of 26; \( P = 0.0496; \) Supplementary Fig. S2C). Although it is more difficult to define the duration of tumor dormancy in this tumor model, judging from earlier studies in which the impact on host immunity (e.g., perforin, TRAIL, IFN, and NKT cells) has been observed on tumor incidence over the first 300 to 500 days of life of these mice (17–20), these data supported the concept that host adaptive immunity controls outgrowth of tumors, even late in life, in tumor prone p53\(^{+/−}\) mice.

**Anti-IL-23p19 reduces malignant potential of MCA-induced stable masses**

Given that IL-12p40 mAb blockade results in the outgrowth of stable masses in MCA-treated C57BL/6 WT mice (7), it was possible that either IL-23 or IL-12 might be responsible for controlling the outgrowth of equilibrium lesions. In the absence of a method to conditionally and specifically delete IL-12p70 heterodimer, we used an IL-23–specific anti-IL-23p19 mAb to assess the comparative effect of neutralizing IL-23 versus IL-12/23p40 in mice harboring stable masses that had been induced by MCA. As in earlier experiments, mice that developed a progressively growing primary tumor up to 200 days were excluded. We then treated mice lacking clinically apparent tumors for 6 weeks with either anti-IL-23p19, anti-IL-12/23p40 mAbs, or control Ig (anti-AGP3), ceased treatment for 3 weeks and then treated the cohorts with either cIg or anti-IFN-γ for an additional 6 weeks (Fig. 2). Specifically, fewer...
tumors developed and tumor appearance displayed delayed kinetics in mice pretreated with anti-IL-23p19 (3 of 18; Fig. 2F) than with cIg (7 of 18; Fig. 2B) after IFN-γ neutralization, suggesting that IL-23 promotes cancer persistence and tumor maintenance during the equilibrium phase and that blockade of IL-23 with anti-IL-23p19 is host-protective. In contrast to cIg (0 of 18) or anti-IL-12p40 (0 of 18) pretreatment, mice receiving anti-IL-12/23p40 developed tumors before secondary cIg (5 of 17) or anti-IFN-γ (5 of 18) treatment, confirming the role of IL-12 in preventing the outgrowth of occult primary cancer cells. Additional tumors grew out in mice initially treated with anti-IL-12p40 and subsequently treated with anti-IFN-γ (4 of 13). These data were supported by 2 other similarly constructed experiments (results of all 3 pooled and summarized in Table 1), in which we observed that treatment with anti-IL-23p19 prevented the outgrowth of MCA tumors from mice subsequently treated with anti-IFN-γ. Overall, regardless of whether anti-IFN-γ (P = 0.0036) or anti-CD4/CD8/IFN-γ (P = 0.0087) treatment was used to permit tumor growth and escape from the equilibrium phase, IL-23 blockade had a statistically found effect in protecting the host compared with cIg (Table 1). Furthermore across several experiments in which tumors arose postimmune depletion, anti-IL-23p19 delayed the outgrowth compared to cIg (Supplementary Fig. S3; P < 0.05). Thus, IL-23 promotes cancer persistence during the equilibrium phase, a result that enhances our knowledge of the previously shown role of IL-23 as a potent cancer promoter, enabling the initiation of MCA-induced sarcomas (11).

Other cytokines that activate and polarize T cells do not seem to regulate equilibrium

To further explore the selectivity of IL-12/IL-23 and IFNγ as critical components of the equilibrium phase, we used a similar loss-of-function approach to assess potential roles for other immunomodulatory/proinflammatory cytokines in the process. Mice deficient in TNF and IFNAR1 have been shown to have an elevated incidence of MCA-induced sarcomas (21, 22), indicating that these 2 cytokines are critical players in cancer immunosurveillance. However, the role of TNF in tumor dormancy remains controversial due to contradictory findings.
in studies of tumor dormancy (23, 24). Here, equilibrium was not altered in different cohorts of MCA-treated mice given neutralizing/blocking mAbs to either TNF or the type I IFN receptor (Fig. 3). Similarly, other key cytokines that define T-cell polarity, IL-4 and IL-17RA, also did not critically regulate the equilibrium phase (Fig. 4). Interestingly, however, anti-IL-10R treatment produced slightly fewer tumors and delayed tumor emergence from equilibrium when compared to mice treated with clg (Fig. 4 and Supplementary Fig. S3). This effect was more evident when anti-IL-10R and anti-IL-23p19 were used in combination (0 of 18 tumors emerged from equilibrium after IFN-γ neutralization, versus 5 of 18 anti-IL-10R and 2 of 19 anti-IL-23p19) and suggests that combinatorial anti-IL-10R/IL-23p19 therapy eliminates most, if not all, persistent cancer cells present in occult tumor masses (Fig. 5; Table 1). Nevertheless, these studies pointed to the very special roles of IFNγ, IL-12, and IL-23 in induction/maintenance of the equilibrium phase.

Triggering CD40 mimics IL-23 neutralization

Because IL-12 is reported to maintain MCA sarcomas in equilibrium to a similar degree as T cells (Fig. 2; ref. 7), we next sought to determine whether agonist anti-CD40, a powerful stimulator of IL-12p70 production from antigen presenting cells could eliminate persistent cancer cells in equilibrium lesions. Mice harboring equilibrium tumors that were treated with anti-CD40 for 6 weeks developed fewer (1 of 54) tumors after anti-IFN-γ treatment than the equivalent group treated with clg (8 of 16; Fig. 6), showing a protective effect for anti-CD40 mAb. The reduction in tumor outgrowth was similar or better than that obtained using anti-IL-23p19 (Fig. 2, 5, and Table 1). These data suggested that either blockade of IL-23p19 or a significant induction of IL-12p70 from CD40 stimulation could resolve dormant fibrosarcomas in the equilibrium phase. The role of IL-12p40, and most logically IL-12p70 in the protective effect of anti-CD40, was supported by the impact of additionally neutralizing IL-12p40 plus anti-CD40 in the second stage in which now 3 of 20 tumors arose, and then a further 5 of 17 tumors in the third stage following anti-IFN-γ treatment.

Discussion

This study significantly expands our rudimentary understanding of the mechanisms controlling the immune-mediated dormancy of the equilibrium phase. First, we have shown that the equilibrium phase is a protracted process resulting in long latency from carcinogen inoculation to tumor outgrowth/
escape that may extend for the entire lifetime of the host (up to 850 days in mice). Second, we have determined, for the first time, that IL-23 plays a critical role in opposing the antitumor effects of IL-12 and thus, allows cancer cells to persist in a state of immune-mediated dormancy and prevent cancer cell elimination. Third, we extend and corroborate our previous findings that adaptive immunity maintains occult cancer in an equilibrium state and that the elimination phase and the equilibrium phase are temporally and mechanistically distinct events. Specifically, cytokines known to regulate tumor immunity such as IL-4, IL-17, TNF, and IFN-κβ do not seem to play a critical role in controlling the equilibrium phase. This is despite the fact that many of these cytokines are critical for the initiation or elimination of MCA-induced sarcomas. Collectively, these data support a model of tumor development and immune system interactions occurring in 3 distinct phases as we have previously described (1, 2), but suggest that specific cytokines such as IL-12 and IL-23 play roles during the earlier

Figure 4. IL-10, but not IL-4 or IL-17, regulates tumors in equilibrium. Groups of 18–20 male C57BL/6 WT mice were inoculated subcutaneously with 10 μg MCA. At day 161–163 the tumor-free mice were injected weekly for 6 weeks (until day 196–198) with cIg (A, B), anti-IL-4 (C, D), anti-IL-17RA (E, F), or anti-IL-10R (300 μg i.p.; G, H). Mice then received cIg (250 μg i.p.; A, C, E, G) or anti-IFN-γ weekly (250 μg i.p.; B, D, F, H) for 6 weeks from day 212–217 to day 247–252. Mice were monitored for the appearance of late-forming sarcomas until day 400 after MCA inoculation. The proportion of tumors arising before and post each mAb treatment are indicated. Tumor size (cm²) for each individual mouse is plotted.
phase of tumor initiation and elimination as well determining the dormancy or outgrowth of occult neoplasia during the equilibrium phase.

We (11) and others (10, 25) have recently shown the effect of IL-23 in suppressing both innate and adaptive antitumor effector responses, and we speculate that local tumor infiltrating myeloid cell production of IL-23 and IL-10 quite possibly directly or indirectly suppresses these antitumor activities. It will be important to determine that leukocytes potentially produce these cytokines and demonstrably regulate the process. In our preliminary studies, because CD11b macrophages produce IL-23 and IL-10 (25, 26), we administered either vehicle control liposomes or the macrophage depleting agent clodrolip (27) before treating the mice with cIg or anti-IFN-γ (Supplementary Fig. S4). Depletion of macrophages abrogated most fibrosarcoma outgrowth (4 of 36) when compared with cIg pretreatment (7 of 16 tumors), suggesting that macrophages were promoting the survival of dormant tumors.

Figure 5. IL-23 and IL-10R blockade collectively resolve equilibrium lesions. Groups of 18–20 male C57BL/6 WT mice were inoculated subcutaneously with 10 μg MCA. At day 161, the tumor-free mice were injected weekly for 6 weeks (until day 196) with cIg (anti-AGP3; A, B), anti-IL-23p19 (C, D), anti-IL-10R (E, F), or anti-p19 and anti-IL-10R (500 μg i.p. each; G, H). Mice then received cIg (A, C, E, G) or anti-IFN-γ (B, D, F, H) weekly (250 μg i.p.) for 6 weeks from day 217 to day 252. Mice were monitored for the appearance of late-forming sarcomas until day 400 after MCA inoculation. The proportion of tumors arising before and post each mAb treatment is indicated. Tumor size (cm²) for each individual mouse is plotted.
fibrosarcomas during the equilibrium phase. In contrast, depletion of CD11c\(^{+}\) cells (including most DC) using diptheria toxin and CD11c DOG transgenic mice, or Ly-6G\(^{+}\) cells (neutrophils) in WT mice did not alter equilibrium tumor outgrowth after anti-IFN-\(\gamma\) treatment (Supplementary Fig. S5). However, although it is true that these depleting antibodies, liposomes, and transgenic mice are the best available tools to eliminate these leukocyte subsets, we realize that these approaches have limited specificity and that deleting these cells may have immune modulating effects that interfere with the establishment of the equilibrium phase. Future studies that specifically delete DCs and other myeloid and granulocyte subsets will be required to elucidate the precise roles these subsets have in generating and maintaining occult tumor cells in equilibrium with antitumor immunity.

Anti-IL-12/23p40 therapies are highly effective in treating psoriasis (28, 29). However, from our studies it is clear there may be a potential risk of compromising cancer surveillance mechanisms through blocking IL-12. More research is needed into the long-term effects of anti-IL-12/23p40 agents in mice, and soon data in humans will be available. Ustekinumab (anti-human IL-12/23p40 antibody, Stelara) is approved in Canada, Europe, and the United States to treat moderate to severe plaque psoriasis. Thus far it has proven both effective and safe. Briakinumab (anti-human IL-12/23p40, ABT-874) has also been tested in patients with psoriasis, including higher dosing, but despite the report of highly promising efficacy (13), it has been withdrawn from U.S. Food and Drug Administration consideration likely due to safety concerns including an imbalance between briakinumab and placebo in serious infections, major adverse cardiac events, and skin cancers (30). IL-12/23p40 antibodies have also shown promise in early clinical trials in Crohn disease (31) and ustekinumab is currently in clinical trials for Crohn disease (Clinical trials identifiers: NCT01369342, NCT01369329, NCT01369355). IBD is associated with increased expression of IL-23 (32) and polymorphisms within the IL-23R gene locus are linked to susceptibility to Crohn disease (33). People who suffer from ulcerative colitis or Crohn disease are at an increased risk of developing colon cancer. It is not yet clear whether inhibition of IL-12/23p40 may increase the risk of cancer in this patient population. Anti-IL-23 mAbs are currently in clinical trials for the treatment of
psoriasis (Clinical trials identifier NCT01225731). We should soon be able to evaluate the therapeutic potential of neutralizing IL-23 in patients with IBD, and it will be interesting to monitor these patients long term for malignancies. Given our data herein, and others concerning the role of IL-23 in tumor initiation, anti-IL-23p19 mAb therapy may be seriously considered for use in a tumor preventative setting. Indeed, the ability of anti-CD40 to prevent tumors emerging from equilibrium suggests there may be some merit in preventing tumor outgrowth by using a combination of anti-CD40 and anti-IL-23p19.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: M.W.L. Teng, R.D. Schreiber, M.J. Smyth
Development of methodology: R.D. Schreiber
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.W.L. Teng, M.D. Vesely, N. McLaughlin, R.D. Schreiber, M.J. Smyth
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.W.L. Teng, M.D. Vesely, R.D. Schreiber, M.J. Smyth
Writing, review, and/or revision of the manuscript: M.W.L. Teng, M.D. Vesely, J.E. Towne, R.D. Schreiber, M.J. Smyth
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.W.L. Teng, H. Duret, N. McLaughlin, M.J. Smyth
Study supervision: M.J. Smyth

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References

Table 1. IL-23 maintains malignant potential of tumors in equilibrium

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NOTE: Composite of data from Figs. 2, 5, and Supplementary Fig. S4, showing the number of mice with tumor outgrowth versus those remaining tumor free following intervention with cIg, anti-IFN-γ, or anti-CD4/CD8/IFN-γ cocktail (stage III). Statistical analysis was carried out by Fishers Exact test, compared against equivalent α-AGP3 group, *, P = 0.0036, **, P = 0.0087, ***, P = 0.2056, ****, P = 0.0007.


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