Published OnlineFirst June 30, 2009; DOI: 10.1158/0008-5472.CAN-09-1351

Polyps Wrap Mast Cells and Treg within Tumorigenic Tentacles

□□ Commentary re: Gounaris et al. Cancer Res 2009;69:5490–7.

Mario P. Colombo and Silvia Piconese

Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico "Istituto Nazionale dei Tumori," Milan, Italy

Abstract

Gounaris and colleagues describe a previously unrecognized cross-talk between mast cells and Treg in colon adenomatous polyposis (Gounaris et al., Cancer Res 2009;69:5490–7). Adoptively transferred Treg suppress the focal mastocytosis that fosters tumor initiation and progression. In contrast, endogenous Treg, which abundantly infiltrate polyps, show proinflammatory activity under unknown microenvironmental cues that promote mast cell differentiation and expansion. Compartmentalized Treg plasticity seems to be a key factor in establishing the optimal milieu for cancer development in the intestines. Treg partnership with mast cells recapitulates the complexity of innate-adaptive networks characterizing gut inflammation and represents a novel target for cancer immunotherapy. [Cancer Res 2009;69(14):5619–22]

Gut, as other mucosal tissues exposed to the external environment, is a site where inflammation and cancer are tightly linked. Bacterial infections, exposure to toxic molecules damaging the epithelial barrier, genetic predisposition, and enhanced immune reactivity, may promote chronic colitis that induces epithelial cell proliferation, stroma remodeling, neoangiogenesis, and suppression of the antitumor adaptive response (1).

Regulatory T cells (Treg) play nonredundant roles in colitis (2, 3). The intestinal Treg pool includes naturally arising $CD4^+Foxp3^+$ Treg, thymus-derived and endowed with a self-directed antigenic repertoire, and also adaptive Treg, developing in the gut upon encounter with foreign antigens under transforming growth factor (TGF)-β and retinoic acid exposure (4). Although systemic Treg suppress immune responses through an array of different mechanisms, the inhibitory function of intestinal Treg is critically dependent on interleukin (IL)-10, especially under microbial triggers (5). Treg activity under homeostatic conditions is as crucial as Treg inactivation when response to pathogens must initiate. TLR ligands and inflammatory cytokines can paralyze Treg functions directly or indirectly, by turning tolerogenic antigen-presenting cells into immunogenic cells that no longer sustain Treg-mediated suppression (6). Under precise microenvironmental stimuli, Treg may be not only "deactivated" but also "reprogrammed" toward alternative differentiation pathways, for instance skewed into IL-17–producing T cells (Th17; ref. 7). Since the discovery of Foxp3 as their master transcription factor, Treg have been considered as a committed lineage, but many data support the idea that Treg can adapt to external and internal challenges with high plasticity and heterogeneity. Distinct Treg subsets, expressing T helper–associated transcription factors, selectively suppress different effector responses (8, 9). It could be predicted that specialized Treg and Teff subsets develop in parallel under different microenvironmental stimuli to maximize immunity and minimize collateral damage (10). A forced conversion of "hybrid" Treg into the corresponding class of effector cells may lie behind pathologic conditions (10).

In tumor immunology, Treg are viewed as one of the major obstacles to the endogenous antitumor immunity and to successful immunotherapy. High Treg frequency, observed in a variety of human and murine cancers, has been associated with poor prognosis (11). Immunotherapeutic strategies aimed at Treg depletion and/or inactivation, as a single approach or in combination with conventional treatments, have shown to significantly improve antitumor response (12). The case of Treg involvement in colon carcinogenesis is unique. Studies from the Erdman's group have shown that transfer of Treg prevents cancer development associated to colitis, induced by microbial infection or by genetic susceptibility to polyposis in Apc^{Min} mice, an effect dependent on IL-10 acting on cells of the innate response (13–15). From a clinical point of view, high-density Treg infiltration in colorectal cancer tissue has been associated to better prognosis, in sharp contrast with other types of solid cancers (16). It could be argued that, during cancer progression, Treg may exert two opposing roles, the suppression of tumor immunity and the inhibition of inflammation; the former occurs in the majority of solid cancer, whereas the latter may be relevant during the carcinogenetic processes fostered by inflammatory conditions. This latter event is not restricted to colorectal but extended to prostatic cancer spontaneously arising in Apc^{Min} mice, a context in which the adoptive transfer of Treg decreases inflammation and protects from tumor development (17).

Among the innate myeloid cells partnering Treg activities, mast cells are gaining new interest. Mast cells produce a wide array of molecules and express panoply of surface receptors that allow interactions with all immune cells (18). In the forefront of immune reactions, they release very rapidly the prepackaged granules containing early-response mediators, while synthesizing *ex novo* second-phase molecules. In recent years, mast cells have been recognized to play immunoregulatory, beside immunostimulatory, functions, mainly through the secretion of IL-10 (19). In spite of their relative paucity in tissues, mast cells play nonredundant and complex roles not only in allergy, but also in autoimmune diseases, allograft tolerance, and cancer (20). Mastocytosis is quite commonly associated to neoplasia. Lisa Coussens and coworkers (21, 22) first showed that mast cells, recruited early into skin cancer, support tumor growth by favoring neoangiogenesis and invasiveness through matrix metalloproteinase 9 secretion. Tumor-associated mast cells favor tumor growth not only participating to stroma remodeling, but

Requests for reprints: Mario P. Colombo, Molecular Immunology Unit, Department of Experimental Oncology, Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico "Istituto Nazionale dei Tumori," Via Venezian 1 20133 Milan, Italy. Phone: 39-02-2390-2252; Fax: 39-02-2390-2630; E-mail: mario.colombo@istitutotumori.mi.it.

doi:10.1158/0008-5472.CAN-09-1351

Published OnlineFirst June 30, 2009; DOI: 10.1158/0008-5472.CAN-09-1351

also exerting immunoregulatory functions on adaptive antitumor response, thus behaving as tolerogenic cells (23).

In this issue, Gounaris and colleagues (24) describe the molecular and cellular loops coiling mast cells and Treg in intestinal polyposis. Based on the premises that adoptively transferred Treg suppress polyposis in the Apc^{Min} model (15) and that mastocytosis is a necessary event to polyp outgrowth in $Apc^{\Delta 468}$ mice (25), the authors show that the two events are causally related. Indeed, transferred Treg were able to suppress focal mastocytosis *in vivo* and to inhibit mast cell progenitor differentiation and expansion *in vitro*. Strikingly, polyps were populated by high numbers of endogenous Treg, which were anergic and suppressive *ex vivo*, while unable to counteract mastocytosis and polyposis "from the inside." IL-10 has been identified as the discriminating molecule that, produced by exogenous and not by endogenous Treg, suppressed *in vitro* mast cell differentiation. However, the definitive prove of the essential role of Treg-derived IL-10 in suppressing polyposis, mainly through the inhibition of focal mastocytosis, *in vivo*, is still lacking. Endogenous Treg from polyp-ridden mice not only failed to inhibit, but also enhanced, mast cell differentiation *in vitro*, suggesting that IL-10 deficit alone could not account for the overall effect. Of note, endogenous Treg displayed not only defective IL-10 secretion but also high IL-17 production. IL-17, but also other molecules produced by polyp-infiltrating Treg, may actively recall mast cell *in vivo*. Thus, locally diverted Treg may help tumor growth through the arrangement of a mast cell–supported proinflammatory microenvironment.

This picture raises the intriguing and topical issue of which factors are redirecting Treg conventional suppressive ability into tissue-restricted proinflammatory activity. Tumor cells, but also infiltrating immune cells, may produce cytokines capable to induce Treg diversion. It could be even suggested that mast cells themselves may be responsible for IL-10 decline and/or IL-17 promotion in polyp-infiltrating Treg. Mast cell–derived tumor necrosis factor (TNF)-α was shown necessary for IL-17 induction in T cells in a mouse model of neutrophilic airway inflammation (26) and may play a similar role in polyposis. Accordingly, the same authors have shown huge TNF-α secretion by polyp-infiltrating mast cells (25). We also have data showing that mast cells can break Treg suppression and anergy *in vitro* and redirect Treg toward Th17 cells,[1] supporting the notion of mast cells sustaining Th17-mediated immune responses. In a mouse model of hepatocarcinoma, mast cells, massively recruited by tumor-derived stem cell factor (SCF), create an inflammatory microenvironment in which both Treg and Th17 cells can expand thus establishing immunosuppression (27). Therefore, a positive feedback between mast cells and Treg may exist in polyps, with mast cells "reprogramming" Treg toward inflammation and Treg, in turn, recalling additional mast cells. Further experiments will elucidate the kinetics of these events and the distinct signals that, acting on Treg or mast cells, initiate the proinflammatory, tumorigenic loop.

The Treg–mast cell interaction has been described at least in other two reports. We take part in describing that Treg inhibit histamine degranulation (but not TNF-α release) in mast cells, through the OX40/OX40L axis, in anaphylaxis (28). The OX40/OX40L pathway, already associated to inflammatory bowel disease (29), deserves a close look in intestinal polyposis. However, Treg preserve TNF-α production in mast cells, an autocrine mechanism known to sustain mast cell precursor proliferation and expansion in the polyps (25). Therefore, Treg may not only recruit mast cells, but also dictate the kind of response that mast cells should arrange locally to maintain inflammation and sustain IL-17 production. Another report from Noelle's group has shown that Treg-infiltrating skin allografts promote, through the production of IL-9, the recruitment of tolerogenic mast cells. Such Treg were described to be fully competent in terms of suppressive function, as capable to release granzyme B against allo-reactive effector T cells *in vivo* (30). It could be argued that, in both grafts and polyps microenvironments, Treg recall mast cells as valuable allies in arranging the tissue-restricted immune response, but their partnership may result in tolerance or inflammation depending on the molecular milieu (Fig. 1).

It remains to be determined whether intestinal Treg directly recruit mast cells in the polyps (possibly through IL-9) or rather promote microenvironmental changes indirectly leading to mastocytosis. Supporting the latter possibility is the observation that adoptive transfer of Treg provokes a general down-regulation of inflammatory signals and, consequently, of mastocytosis. Therefore, still unknown intermediaries may link Treg to mast cells. IL-9, one of the most important growth factor and chemoattractant for mast cells (31), has recently come in the limelight as the master cytokine characterizing a novel T helper subset, developing from naïve T cells in the concurrent presence of IL-4 and TGF-β or from committed Th2 cells upon exposure to TGF-β. The inability to differentiate this subset *in vivo* results in the failure to recruit mucosal mast cells and to eradicate helminth infections in the intestines (32). Future investigation will uncover the role of "Th9" cells in intestinal polyposis, a Th2-biased pathologic condition (33) in which Treg may locally provide the TGF-β necessary to skew Th2 cells into Th9 effector cells. Of note, although IL-10 production has been detected *in vitro* in Th9 cells, *in vivo*, in a mouse model of inflammatory bowel disease, they behave as proinflammatory rather than regulatory (34), suggesting that IL-10 secretion may be inhibited in the colon microenvironment by local inflammatory cues, as occurs for polyp-infiltrating Treg.

Adoptive transfer of Treg is currently considered a suitable preventive and therapeutic option for a variety of autoimmune and inflammatory diseases in humans (35). This idea is supported by many studies in mice showing the protective role of exogenous Treg, colitis included (4). Less clear is the reason why endogenous Treg, abundantly present in inflamed colonic mucosa, fail to prevent pathology. A possible explanation is that Treg, routinely activated during ongoing responses to resolve inflammation eventually, are outcompeted by persistent proinflammatory signals or even subverted into fully armed effector cells despite persistent Foxp3 expression. Very recent is the finding that adoptively transferred Treg lose Foxp3 expression and gain, in the gut, phenotype and function of follicular B-helper T cells, supporting germinal center formation and arranging the main networks of intestinal immunity (36). It would be of interest to study if exogenous Treg may modulate the germinal center response also in intestinal polyposis, a condition correlated to IgA-mediated humoral immune reactivity (33). In light of the novel findings about Treg transcriptional and functional heterogeneity, it could be suggested that the same local cues skewing the development of a specific class of effector T cells may concurrently promote an exaggerated specialization of the corresponding Treg subset,

[1] S. Piconese, G. Gri, C. Tripodo, et al. Mast cells counteract regulatory T cell suppression through interleukin-6 and OX40/OX40L axis toward Th17 cell differentiation, submitted for publication.

Published OnlineFirst June 30, 2009; DOI: 10.1158/0008-5472.CAN-09-1351

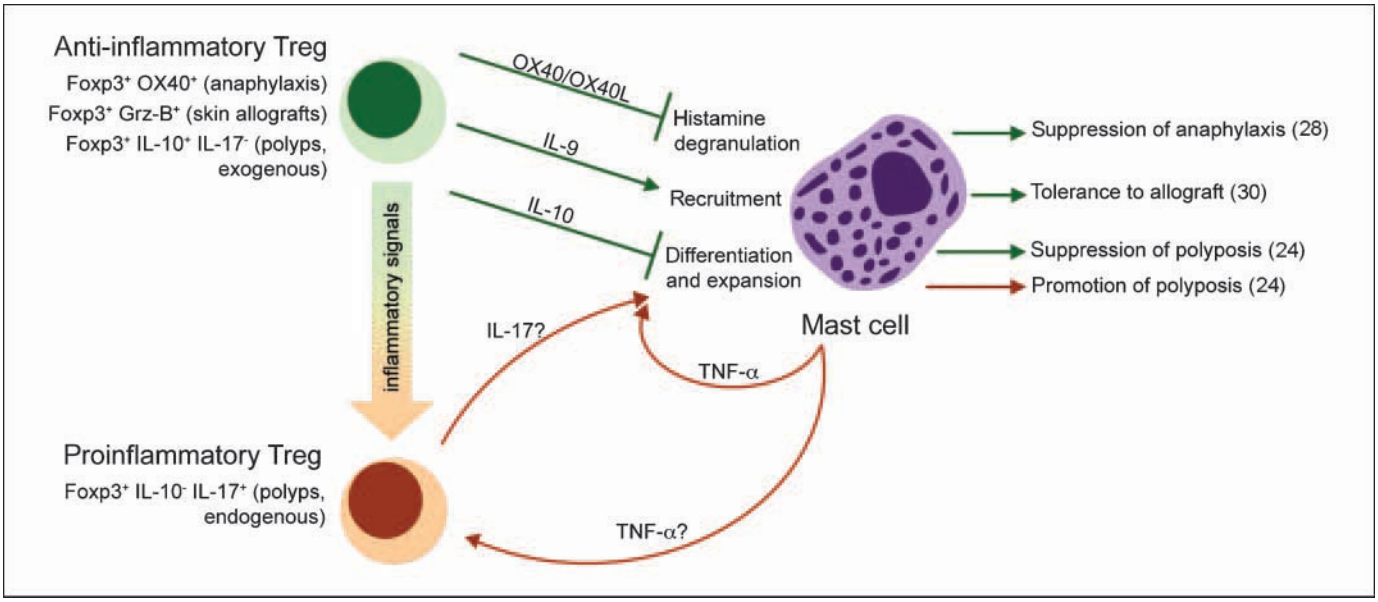

Figure 1. Plasticity of Treg–mast cell interactions. Conventional, anti-inflammatory Treg (*green*) can inhibit immune responses and sustain tolerance interacting with mast cells in several contexts. Through OX40/OX40L-mediated crosstalk, natural Treg suppress histamine degranulation by mast cells, thus controlling systemic anaphylaxis (28). Treg infiltrating skin allografts produce granzyme B to directly suppress T-cell response and secrete IL-9 to recruit tolerogenic mast cells and establish tolerance to alloantigens (30). In a model of colon polyposis, adoptively transferred Treg reach the intestines and produce locally IL-10, thus inhibiting focal mastocytosis and polyposis (24). In contrast, within polyps, microenvironmental cues can convert protective Treg into proinflammatory cells (*orange*), which fail to secrete IL-10 and produce IL-17, thus promoting mast cell recruitment and expansion (24). Polyp-infiltrating mast cells produce huge amount of TNF-α, which not only sustains mastocytosis in an autocrine manner (25) but may also enhance Treg conversion into IL-17–producing cells. IL-17 may, in turn, actively increase mastocytosis thus creating a positive-feedback loop.

impairing the correct regulatory program. Mast cells, thought to contribute to the differentiation of different T helper subsets (18), may act also on specific Treg subsets exacerbating their plasticity.

The novel immune pathways described by Gounaris and colleagues (24) in colon polyposis offer new therapeutic targets and provide additional explanations for the efficacy of old treatments. Cyclooxygenase (COX)-2 inhibitors are one of the most promising drugs for the treatment of gastrointestinal malignancies. It should be noted that their efficacy may rely also on the inhibition of Th17 differentiation in the colon, as prostaglandin-E2 has been recently shown to promote Th17 skewing (37). Administration of tyrosine kinase inhibitors, such as imatinib mesylate, may lead to successful cancer treatment also by directly targeting SCF-mediated mast cell migration and activation *in vivo*, as recently shown in murine and human neurofibromatosis (38). Also, dietary restriction may help inhibiting IL-17 induction in T cells; for instance, retinoic acid assumption negatively impacts Th17 differentiation while promoting Treg induction (39). Last but not least, exposure to pollutants can alter immune homeostasis; indeed, stimulation of the aryl hydrocarbon receptor, a molecule involved in the toxicity of dioxin, increases Th17 differentiation and effector functions in autoimmunity (40).

In a mouse model of colitis-associated carcinogenesis, TNF-α blockade decreased the recruitment of inflammatory cells, the expression of COX-2 and the incidence of cancer (41). Results of phase I and II clinical trials indicate that TNF-α antagonist etanercept or the antibody infliximab have some therapeutic activity against metastatic breast cancer (42), ovarian cancer (43), renal cell carcinoma (44), melanoma, and also colorectal cancer (45), although the involvement of Treg and Th17 in such settings remains to be investigated. Of note, blockade of TNF-α induces fully suppressive Treg in patients of rheumatoid arthritis (46), while rapidly reducing the Th17 response in psoriatic plaques (47). Interestingly, murine tumor-infiltrating Treg were found to express huge levels of TNF receptor II (48), suggesting that TNF-α may exert its protumorigenic role also through Treg expansion and activation.

The mast cell–Treg interaction offers novel therapeutic targets in inflammatory disease and cancer. On one side, the inhibition of Treg-promoted mastocytosis could be obtained blocking the relevant cytokines, such as IL-17 and IL-9, likely involved in mast cell recruitment and expansion. On the other side, mast cell–induced Treg deprogramming could be prevented by the selective inhibition of proinflammatory molecules, such as TNF-α, IL-23, and IL-6, or by the generalized blockade of mast cell degranulation with a mast cell stabilizer such as cromolyn. Finally, molecules involved in direct Treg–mast cell crosstalk, such as the OX40/OX40L axis, could be targeted to functionally tune the relevant pathways at the crossroad of the innate and the adaptive immune response.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

Received 4/10/09; revised 6/9/09; accepted 6/17/09; published OnlineFirst 6/30/09.

We thank Associazione Italiana per la Ricerca sul Cancro, Italian Ministry of Health and Istituto Superiore di Sanità within the Alliance Against Cancer Program, for financial support. S. Piconese is supported by a fellowship from Fondazione Italiana per la Ricerca sul Cancro.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Published OnlineFirst June 30, 2009; DOI: 10.1158/0008-5472.CAN-09-1351

References

1. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–7.
2. Bennett CL, Christie J, Ramsdell F, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 2001;27:20–1.
3. Sharma R, Sung SS, Fu SM, Ju ST. Regulation of multi-organ inflammation in the regulatory T cell-deficient scurfy mice. J Biomed Sci 2009;16:20.
4. Izcue A, Coombes JL, Powrie F. Regulatory lymphocytes and intestinal inflammation. Annu Rev Immunol 2009;27:313–38.
5. Rubtsov YP, Rasmussen JP, Chi EY, et al. Regulatory T cell-derived interleukin-10 limits inflammation at environmental interfaces. Immunity 2008;28:546–58.
6. Belkaid Y, Tarbell KV. Arming Treg cells at the inflammatory site. Immunity 2009;30:322–3.
7. Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 2006; 441:235–8.
8. Koch MA, Tucker-Heard G, Perdue NR, Killebrew JR, Urdahl KB, Campbell DJ. The transcription factor T-bet controls regulatory T cell homeostasis and function during type 1 inflammation. Nat Immunol 2009;10:595–602.
9. Zheng Y, Chaudhry A, Kas A, et al. Regulatory T-cell suppressor program co-opts transcription factor IRF4 to control T(H)2 responses. Nature 2009;458:351–6.
10. Barnes MJ, Powrie F. Hybrid Treg cells: steel frames and plastic exteriors. Nat Immunol 2009;10:563–4.
11. Curiel TJ. Tregs and rethinking cancer immunotherapy. J Clin Invest 2007;117:1167–74.
12. Colombo MP, Piconese S. Regulatory-T-cell inhibition versus depletion: the right choice in cancer immunotherapy. Nat Rev 2007;7:880–7.
13. Erdman SE, Rao VP, Poutahidis T, et al. CD4(+)CD25(+) regulatory lymphocytes require interleukin 10 to interrupt colon carcinogenesis in mice. Cancer Res 2003;63:6042–50.
14. Erdman SE, Poutahidis T, Tomczak M, et al. CD4+ CD25+ regulatory T lymphocytes inhibit microbially induced colon cancer in Rag2-deficient mice. Am J Pathol 2003;162:691–702.
15. Erdman SE, Sohn JJ, Rao VP, et al. CD4+CD25+ regulatory lymphocytes induce regression of intestinal tumors in ApcMin/+ mice. Cancer Res 2005;65:3998–4004.
16. Salama P, Phillips M, Grieu F, et al. Tumor-infiltrating FOXP3+ T regulatory cells show strong prognostic significance in colorectal cancer. J Clin Oncol 2009;27: 186–92.
17. Poutahidis T, Rao VP, Olipitz W, et al. CD4+ lymphocytes modulate prostate cancer progression in mice. Int J Cancer 2009;125:868–78.
18. Sayed BA, Christy A, Quirion MR, Brown MA. The master switch: the role of mast cells in autoimmunity and tolerance. Annu Rev Immunol 2008;26:705–39.
19. Galli SJ, Grimbaldeston M, Tsai M. Immunomodulatory mast cells: negative, as well as positive, regulators of immunity. Nat Rev Immunol 2008;8:478–86.
20. Theoharides TC, Conti P. Mast cells: the Jekyll and Hyde of tumor growth. Trends Immunol 2004;25:235–41.
21. Coussens LM, Raymond WW, Bergers G, et al. Inflammatory mast cells up-regulate angiogenesis during squamous epithelial carcinogenesis. Genes Dev 1999; 13:1382–97.
22. Coussens LM, Tinkle CL, Hanahan D, Werb Z. MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis. Cell 2000;103:481–90.
23. Wasiuk A, de Vries VC, Hartmann K, Roers A, Noelle RJ. Mast cells as regulators of adaptive immunity to tumours. Clin Exp Immunol 2009;155:140–6.
24. Gounaris L, Blatner NR, Denis K, et al. T-regulatory cells shift from a protective anti-inflammatory to a cancer-promoting pro-inflammatory phenotype in polyposis. Cancer Res 2009;69:5490–7.
25. Gounaris E, Erdman SE, Restaino C, et al. Mast cells are an essential hematopoietic component for polyp development. Proc Natl Acad Sci U S A 2007;104:19977–82.
26. Nakae S, Suto H, Berry GJ, Galli SJ. Mast cell-derived TNF can promote Th17 cell-dependent neutrophil recruitment in ovalbumin-challenged OTII mice. Blood 2007;109:3640–8.
27. Huang B, Lei Z, Zhang GM, et al. SCF-mediated mast cell infiltration and activation exacerbate the inflammation and immunosuppression in tumor microenvironment. Blood 2008;112:1269–79.
28. Gri G, Piconese S, Frossi B, et al. CD4+CD25+ regulatory T cells suppress mast cell degranulation and allergic responses through OX40-40L interaction. Immunity 2008;29:771–81.
29. Malmstrom V, Shipton D, Singh B, et al. CD134L expression on dendritic cells in the mesenteric lymph nodes drives colitis in T cell-restored SCID mice. J Immunol 2001;166:6972–81.
30. Lu LF, Lind EF, Gondek DC, et al. Mast cells are essential intermediaries in regulatory T-cell tolerance. Nature 2006;442:997–1002.
31. Zhou Y, McLane M, Levitt RC. Th2 cytokines and asthma. Interleukin-9 as a therapeutic target for asthma. Respir Res 2001;2:80–4.
32. Veldhoen M, Uyttenhove C, van Snick J, et al. Transforming growth factor-β 'reprograms' the differentiation of T helper 2 cells and promotes an interleukin 9-producing subset. Nat Immunol 2008;9:1341–6.
33. Kettunen HL, Kettunen AS, Rautonen NE. Intestinal immune responses in wild-type and Apcmin/+ mouse, a model for colon cancer. Cancer Res 2003;63:5136–42.
34. Dardalhon V, Awasthi A, Kwon H, et al. IL-4 inhibits TGF-β-induced Foxp3+ T cells and, together with TGF-β, generates IL-9+ IL-10+ Foxp3(−) effector T cells. Nat Immunol 2008;9:1347–55.
35. Allan SE, Broady R, Gregori S, et al. CD4+ T-regulatory cells: toward therapy for human diseases. Immunol Rev 2008;223:391–421.
36. Tsuji M, Komatsu N, Kawamoto S, et al. Preferential generation of follicular B helper T cells from Foxp3+ T cells in gut Peyer's patches. Science 2009; 323:1488–92.
37. Boniface K, Bak-Jensen KS, Li Y, et al. Prostaglandin E2 regulates Th17 cell differentiation and function through cyclic AMP and EP2/EP4 receptor signaling. J Exp Med 2009;206:535–48.
38. Yang FC, Ingram DA, Chen S, et al. Nf1-dependent tumors require a microenvironment containing Nf1+/− and c-kit-dependent bone marrow. Cell 2008;135:437–48.
39. Mucida D, Park Y, Kim G, et al. Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. Science 2007;317:256–60.
40. Veldhoen M, Hirota K, Westendorf AM, et al. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature 2008;453: 106–9.
41. Popivanova BK, Kitamura K, Wu Y, et al. Blocking TNF-α in mice reduces colorectal carcinogenesis associated with chronic colitis. J Clin Invest 2008;118:560–70.
42. Madhusudan S, Foster M, Muthuramalingam SR, et al. A phase II study of etanercept (Enbrel), a tumor necrosis factor α inhibitor in patients with metastatic breast cancer. Clin Cancer Res 2004;10:6528–34.
43. Madhusudan S, Muthuramalingam SR, Braybrooke JP, et al. Study of etanercept, a tumor necrosis factor-α inhibitor, in recurrent ovarian cancer. J Clin Oncol 2005; 23:5950–9.
44. Harrison ML, Obermueller E, Maisey NR, et al. Tumor necrosis factor α as a new target for renal cell carcinoma: two sequential phase II trials of infliximab at standard and high dose. J Clin Oncol 2007;25:4542–9.
45. Brown ER, Charles KA, Hoare SA, et al. A clinical study assessing the tolerability and biological effects of infliximab, a TNF-α inhibitor, in patients with advanced cancer. Ann Oncol 2008;19:1340–6.
46. Nadkarni S, Mauri C, Ehrenstein MR. Anti-TNF-α therapy induces a distinct regulatory T cell population in patients with rheumatoid arthritis via TGF-β. J Exp Med 2007;204:33–9.
47. Zaba LC, Cardinale I, Gilleaudeau P, et al. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. J Exp Med 2007;204:3183–94.
48. Chen X, Subleski JJ, Kopf H, Howard OM, Mannel DN, Oppenheim JJ. Cutting edge: expression of TNFR2 defines a maximally suppressive subset of mouse CD4+CD25+FoxP3+ T regulatory cells: applicability to tumor-infiltrating T regulatory cells. J Immunol 2008; 180:6467–71.

Cancer Research
The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

AACR American Association for Cancer Research

Polyps Wrap Mast Cells and Treg within Tumorigenic Tentacles

Mario P. Colombo and Silvia Piconese

Cancer Res 2009;69:5619-5622. Published OnlineFirst June 30, 2009.