Regulatory T-cell heterogeneity and the cancer immune response

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The frequency of circulating or tumour-infiltrating regulatory T cells (Tregs) has been associated with poor patient survival in many cancers including breast, melanoma and lung. It has been hypothesised that Tregs impact the anti-tumour function of effector T cells, resulting in worse outcomes for patients. However, high infiltrates of Tregs have been associated with a positive outcome of patients in a minority of cancers including colorectal, bladder and oesophageal. In addition, many studies have shown no impact of Tregs in patient outcome. Traditionally, research has identified Tregs as forkhead box P3 (FOXP3+) T cells in order to make such associations. Recently, it has become evident that regulatory populations are very heterogeneous, and this heterogeneity is essential for Treg function. Treg heterogeneity likely affects predictions of patient outcome, and different Treg populations may have different influences on tumours. The study of Tregs in cancer must include a better definition of the cells analysed. This review will focus primarily on colorectal cancer in humans, due to mixed data on the impact of Tregs on patient outcome in this disease.

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INTRODUCTION

Regulatory T cells (Tregs) are essential for the suppression of self-reactive T cells in the periphery and the inhibition of immune responses at the resolution of infection.1 Historically, Tregs were divided into two groups, those formed in the thymus (natural), and those differentiated in the periphery (induced). The transcription factor, Helios, has been used as a marker to distinguish natural and induced Tregs, but expression of Helios has been identified on both populations in humans.2

Tregs are characterised by high expression of the interleukin two receptor (IL-2R) alpha, CD25 and expression of the transcription factor, FOXP3,1 both of which are essential for their regulatory functions. The expression of CD25 on FOXP3+ Tregs is believed to facilitate sequestration of IL-2 from the environment, thereby reducing effector T-cell access to IL-2.3 FOXP3 expression is critical for the suppressive function of Tregs: mutations in the FOXP3 gene cause fatal autoimmune disease and immunopathology in humans.4 CD25 and FOXP3 alone cannot be used to identify Tregs, as conventional T-cell populations can upregulate both of these markers after activation.5 However, demethylation of the FOXP3 locus occurs only in Tregs with stable expression of FOXP3 and not conventional T cells that upregulate FOXP3 transiently after activation.6 Tregs in humans, at least in the blood, also express low levels of CD127 and use of this molecule alongside FOXP3 and CD25 has been proposed as a more accurate means of identifying Tregs.7,8

In addition to the inhibition of effector T-cell activation and proliferation via the sequestration of IL-2, Tregs can suppress effector T cells using other mechanisms. Tregs secrete suppressive cytokines, such as IL-10, IL-35 and transforming growth factor (TGF)-β, express inhibitory markers such as cytotoxic T-lymphocyte-associated protein (CTLA)-4 and inducible T-cell costimulator (ICOS) that inhibit the ability of antigen presenting cells to activate effector T cells, and cause apoptosis of effector cells via the production of granzyme (reviewed in Vignali et al.9). In cancer patients, tumour-infiltrating Tregs often express higher levels of inhibitory markers and are much more suppressive than Tregs from peripheral blood mononuclear cells (PBMCs) or from non-tumour tissue. This is most likely due to factors within the tumour microenvironment.10

Tregs are often identified using FOXP3 alone in studies of people with cancer, sometimes without including a T-cell marker. This approach is often dictated by the sample type and availability, however, it is clear that this is not sufficient to identify heterogeneous T-cell populations with regulatory function. For example, we recently showed no association with Tregs and outcome in a cohort of colorectal cancer (CRC) patients when identified by T-cell expression of FOXP3 alone. However, when the transcription factor, B lymphocyte-induced maturation protein-1 (Blimp-1), was used alongside FOXP3 to identify a subpopulation of Tregs, there was a positive association with patient outcome.11 In a cohort of patients with B-cell lymphoma, a high infiltrate of Tregs identified by expression of FOXP3 alone was associated with good patient outcome, but CTLA-4+FOXP3+ double-positive Tregs were associated with poor patient outcome.12 These results emphasise the importance of using more than one marker to identify Tregs in human cancer tissue.
**EFFECTOR TREGS**

FOX3+ Tregs have been proposed to exist in multiple differentiation states, similar to effector T-cell populations: naive, effector and memory. Two functionally distinct phenotypes of suppressive FOX3+ Tregs have been identified in human blood: CD45RA+FOX3+ "naive" Tregs and CD45RA-FOXP3+ "effector" Treg populations. It is likely that these naive-like Tregs were thymic derived, resting Tregs that once activated, converted to effector-like activated Tregs.

In mice, the term 'effector Tregs' (eTregs) has been given to a similar population of FoxP3+ Tregs that express Blimp-1 (reviewed in Cretney et al.). These eTregs have high expression of many Treg activation markers including CTLA-4, ICOS, CD45R0, and are highly suppressive. Blimp-1 and interferon regulatory factor (IRF)-4 were essential for the development of FoxP3+ eTregs, and Blimp-1 was essential for IL-10 production in T cells. FXO3+ eTregs were present in the gut of mice and have been identified in human CRC. We have recently demonstrated that Blimp-1 can be used to identify a similar population of Tregs in humans with an effector phenotype (unpublished).

Memory Treg populations are not well understood. In mice, FoxP3+ Tregs specific for self-antigen, viral antigen or foetal antigen showed similar characteristics to effector memory T cells: an expansion during primary response, a small remaining population, and then expansion during a secondary response. In humans it is more challenging to study an antigen-specific Treg response over time to measure memory, but using phenotypic markers based on effector memory T cells, a population of memory-like FOXP3+CD25+Tregs (CD45RO+ICOS+CD27+CTLA-4+) has been identified in human skin.

The tumour microenvironment contains Tregs with an effector phenotype in many human cancers, and this is likely in response to inflammatory factors produced by other cells interacting with Tregs within this environment (reviewed in Chaudhary and Elkord). However, other studies demonstrate conflicting evidence. Saito et al. indicated that FOXP3+ eTregs, but not FOXP3- Tregs, were associated with poor patient outcomes in CRC. Lin et al. demonstrated that Tregs with an effector phenotype (FOXP3+CD45RA-), but not a resting phenotype (FOXP3+CD45RA+), were associated with late-stage CRC. Nakayama et al. classified 'effector Tregs' as FOXP3+ CTLA-4+ in a B-cell lymphoma cohort and high infiltrates were associated with poor patient outcomes. These studies indicate that using different markers to define eTreg populations may result in different associations with patient outcomes, and that eTreg infiltrates may have different roles across human cancers.

**HELPER-LIKE TREG SUBSETS**

Treg phenotypes can differ as a result of the environment in which they differentiate, similar to effector T-cell populations. FOXP3+ Tregs upregulate transcription factors that can mirror effector T-cell populations differentiated under the same conditions and influence immune responses (reviewed in Cretney et al.). The transcription factor, signal transducer and activator of transcription (STAT)-3 is essential for the suppression of Th17 inflammatory IL-17 responses in mice. The expression of T-bet in FoxP3+ Tregs is essential for the suppression of Th17 IFN-γ effector responses in mice. Finally, the expression of IRF4 is essential for the suppression of Th12 responses in mice.

FOX3+ Tregs expressing canonical T effector transcription factors, especially RORγt, have been identified in healthy human PBMCs. In mice, RORγt+FoxP3+ Tregs and RORγt+ Th17 cells coexisted in a healthy state and RORγt+FoxP3+ Tregs could suppress intestinal inflammation. RORγt+FOXP3+ Tregs have been identified in CRC patients and were enriched in patients with late-stage cancer. RORγt+ FOXP3+ Tregs were also upregulated in the blood from people with pancreatic cancer, compared to age-matched healthy controls. RORγt+ FOXP3+ Tregs in CRC and pancreatic patients produced both IL-10 and IL-17. These data indicate that perturbations in these populations in cancer may influence disease and potentially contribute to poor outcomes for patients.
suppress the proliferation of CD8+ tumour-infiltrating lymphocytes stimulated with CRC antigens in humans. Supernatant from ex vivo-cultured IL-17+ Tregs from human colitis tissue increased IL-6 and IL-1β production in T cells. Tregs that produced IL-17+ in human CRC tumours lost their ability to suppress mast cell degranulation, and potentially aided growth of cancer initiating cells. Hypoxia-induced FOXP3+ Tregs also produced IL-17 in vitro, this may also occur in the tumour microenvironment. These results indicate that IL-17+ Tregs may be differentiated from T\(\text{H}17\) cells in CRC due to factors in the tumour microenvironment, resulting in the promotion of inflammation and suppression of tumour-specific CD8+ T cells.

**NON-CLASSICAL REGULATORY T-CELL POPULATIONS IN TUMOURS**

**LAP+ Tregs**

Tregs that secrete IL-10 and have low or negative expression of FOXP3 have been identified in multiple cancers (reviewed in Chaudhary and Elkord). Of note, populations of FOXP3+ and FOXP3+ T cells that express latency-associated protein (LAP) have been identified in CRC. The tumour-infiltrating LAP+FOXP3+ cells had 50-fold more suppressive capacity than LAP-FOXP3+ Tregs isolated from the peripheral blood. Infiltrates of LAP+ Tregs were associated with higher tumour, lymph node, metastasis (TNM) stage in this study, indicating that they could be associated with poor patient outcome.

**CD8+ FOXP3+ Tregs**

There is evidence that CD8+ T-cell populations can also express FOXP3 and have regulatory function. CD8+FOXP3+ Tregs have been identified in CRC tissue and were able to suppress CD4+ T-cell proliferation and IFN-γ production ex vivo. CD8+ FOXP3+ Tregs have also been identified in ovarian cancer patients and higher infiltrates were associated with higher stage of disease. Upon co-culture with ovarian tumour cell lines, CD8+ effector T cells converted into CD8+FOXP3+ Tregs. These in vitro-generated CD8+ FOXP3+ Tregs suppressed CD4+ T-cell proliferation. These data indicate that the tumour microenvironment may induce suppressive CD8+ FOXP3+ Tregs.

**TREG FUNCTION IN THE TUMOUR MICROENVIRONMENT**

**Suppression of effector T cells**

Antigen-specific Tregs have been isolated from CRC, pancreatic cancer, bladder cancer and melanoma (reviewed in Chaudhary and Elkord). In advanced melanoma patients, effector T cells and CD25hi Tregs had T-cell receptors specific for the same epitopes. Ex vivo analysis of FOXP3+ Tregs from tumour samples of 15 pancreatic cancer patients revealed that Tregs made up 17% of the T-cell clones that were reactive to tumour peptide enolase 1 (ENO1); these Tregs suppressed the proliferation of ENO1-specific T cells. In a cohort of 62 CRC patients, two-thirds of the patients had effector T cells that were reactive to the CRC antigens, ST4 and carcinoembryonic antigen (CEA). Effector T-cell responses were suppressed by FOXP3+ Tregs from the tumours. In all patients with disease recurrence, FOXP3+ Tregs from the tumours were able to effectively suppress tumour-specific tumour-infiltrating T cells. These results suggest that tumour-specific Tregs and effector T cells co-exist within tumours, and suppression of effector T cells may be associated with poor patient outcome.

**Suppression of T\(\text{H}17\) cells**

High numbers of infiltrating Tregs have been associated with good patient outcomes in multiple cancers, including CRC. It has been hypothesised that this is at least partly due to FOXP3+ Treg-mediated suppression of T\(\text{H}17\) responses that are known to cause unfavourable outcomes in CRC patients. A higher ratio of Tregs to T\(\text{H}17\) cells was associated with lower metastasis scores, and therefore favourable patient outcomes in a cohort of CRC patients. There is also evidence that, in humans, ex vivo naive and memory FOXP3+ Treg populations can inhibit the ability of T\(\text{H}17\) cells to produce the inflammatory cytokines; IL-17 and IL-22.

In mice that lack functional IL-10, severe intestinal inflammation and spontaneous CRC can develop; indicating that IL-10 is involved in the control of inflammation-driven CRC. More recently, others have also demonstrated the importance of IL-10-mediated suppression of inflammatory responses in the colon and in MC38 colon mouse tumour models. Blimp-1 is essential for IL-10 production in Tregs; high frequencies of Blimp-1+FOXP3+ Tregs were recently associated with improved patient outcomes in human CRC. It is possible Blimp-1+ Tregs may suppress inflammatory responses in CRC via the production of IL-10.

**Effect of tumour microenvironment on Treg function**

There is extensive evidence that effector T cells upregulate markers of exhaustion and lose their ability to function in tumours. It is not yet clear whether T-cell exhaustion also occurs in Tregs, especially in the tumour microenvironment. In human glioblastoma tissue, FOXP3+ Tregs expressing programmed cell death protein (PD)-1 were enriched in tumours compared to peripheral blood. Mass cytometry was used to determine the phenotype of PD-1hiFOXP3+ Tregs in human glioblastoma and PD-1hi expression correlated with higher expression of ICOS and lymphocyte activation gene (LAG)-3. PD-1-expressing FOXP3+ Tregs had genetic signatures that correlated with exhaustion and Treg activation. Tregs in tumours of CRC patients also upregulated immunosuppressive markers present on populations of exhausted effector T cells, but these FOXP3+ Tregs were proposed to be activated and highly suppressive due to high expression of CD39 and LAP.

Other immune cells from CRC tumours are able to modulate the function of Tregs. FOXP3+ Tregs from CRC tissue, compared to the same cells from non-tumour tissue, had upregulated expression of genes associated with the promotion of inflammation. Blanter et al. showed that Tregs from human CRC tumours lost the ability to produce IL-10 and instead produced IL-17. These Tregs, although able to suppress effector T-cell proliferation, lost the ability to inhibit the degranulation of mast cells. In CRC, mast cells contribute to tumour growth and angiogenesis, and higher numbers are associated with advanced stage CRC. In vitro stimulation of naïve Tregs with mast cells was sufficient for Tregs to secrete IL-17 and become inflammatory. Therefore, mast cells in CRC may convert Tregs to an inflammatory IL-17 phenotype that promotes inflammation in the tumour microenvironment and aids in tumour progression.

**The tumour site contributes to Treg heterogeneity**

The human gut contains more than 10^{14} bacterial cells. The intestinal epithelium prevents bacteria from entering the mucosa, but this physical barrier can become permeable allowing the entry of bacteria. Once in the mucosa, bacteria encounter immune cells and are able to induce inflammatory responses including T\(\text{H}17\) cells. It has been proposed that the presence of tumours can make the colon more permeable, allowing the infiltration of bacteria-multiple bacterial species have been identified in tumours of CRC patients. Bacteria could promote inflammatory responses in CRC. In mouse models, CD25hi Tregs were able to prevent cancer growth induced by...
bacteria. Therefore, Tregs in CRC may suppress bacteria-driven inflammatory responses such as those mediated by Tp17 cells.

**POTENTIAL FOR CLINICAL INTERVENTION**

The role of Tregs in cancer immunotherapy

Immune checkpoint inhibitors (ICI) are currently being investigated as a cancer treatment and have shown promise in specific cancers such as melanoma. Tregs upregulate multiple ICI receptors (for example, CTLA-4, PD-1) in cancer and the effect of ICI treatment on Treg infiltrates in tumours is unclear. Interestingly, in multiple melanoma clinical trials with ipilimumab (anti-CTLA-4) treatment, Treg numbers in peripheral blood increased and were associated with both poor and favourable patient outcomes. In a small cohort of 10 melanoma patients, the number of FOXP3+ Tregs were measured in response to peptide pools and found to be increased and were associated with both poor and favourable patient outcomes.10 In a small cohort of 10 melanoma patients, the number of FOXP3+ Tregs were measured in response to peptide pools and found to be increased and were associated with both poor and favourable patient outcomes. In a small cohort of 10 melanoma patients, the number of FOXP3+ Tregs were measured in response to peptide pools and found to be increased and were associated with both poor and favourable patient outcomes.10

**Utilisation of beneficial factors from Tregs to treat cancer**

It has been proposed that IL-10 may not be strictly suppressive in the tumour microenvironment and cancer progression: role and therapeutic targeting. Vaccines 2016; 4: 28. 14 Miyara M, Yoshioka Y, Kitoh A, Shimka T, Wing K, Niwa A et al. Functional delineation and differentiation dynamics of CD4+ T cell subsets that contribute to indoleamine 2,3-dioxygenase expression in human colorectal cancer patients: a pilot study. Cancer Immunol Immunother 2017; 66: 515–522.

**SUMMARY AND CONCLUSIONS**

Tregs exist in multiple phenotypes-the heterogeneity and plasticity are common in the tumour microenvironment and may be a contributing factor to disease. This review has summarised Treg sub-populations of interest in human cancer and attempted to link these populations to clinical outcomes. It is clear that the cells and molecules within the tumour microenvironment can alter Treg phenotype and ultimately impact patient survival in cancer patients. A more detailed identification of Treg phenotype is required to fully appreciate the role of Tregs in cancer. We have emphasised that FOXP3 alone is not sufficient to describe Tregs. The addition of more detailed markers, used in conjunction with one another, will allow for a deeper understanding of the role of Tregs in cancer and whether they can be used to improve therapies.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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Treg heterogeneity in cancer
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