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Emerging role of Treg FOXP3 expression in cancer prognosis and autoimmune diseases

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Key point

Recent studies highlighted the promising role of immunohistochemical evaluation of FOXP3 as a routine affordable marker in predicting disease activity of autoimmune diseases and as a prognostic marker for various types of carcinoma.

Regulatory T cells (Tregs), were previously named suppressor T cells. Tregs are immunosuppressive cells that generally suppress the induction and proliferation of effector T cells, maintaining tolerance to self-antigens (1). Tregs express CD4, FOXP3, and CD25 (2). Both effector T cells and Tregs express CD4 and CD25, making it difficult to differentiate between them (3). Thus, FOXP3 expression was used to detect suppressor activity (4).

Tregs are important in maintaining the immune cell homeostasis by enforcing a dominant negative regulation on other immune cells. Tregs are usually classified into natural Tregs CD4+CD25+ T-developing from thymus and induced Tregs which acquire CD25 (IL-2R alpha) expression outside of the thymus and are induced by inflammation and disease processes, like autoimmunity or cancers (5).

In patients having cancer, Tregs tend to be upregulated, and recruited to the site of the tumor. Studies have proved that Tregs suppress the tumor immunity mediated by the host defense (6).

Most tumors induce an immune response in the host by tumor antigens, this causes large numbers of tumor-infiltrating lymphocytes (TILs) to be found in the tumor microenvironment slowing or terminating the tumor development (7). Tregs can make up as much as 20%-30% of the total CD4+ population around the tumor microenvironment (8). High levels of Tregs demonstrated by FOXP3 in the tumor microenvironment indicate poor prognosis in many cancers, like ovarian, breast, renal, and pancreatic cancer (9). In ovarian cancer, high FOXP3 expression was considered as an independent prognostic factor (10). It was also correlated with recurrence in patients of NSCLC at pathologic stage I (11).

On the other hand, in some types of cancer like colorectal carcinoma and follicular lymphoma high levels of Tregs were reported to be associated with good prognosis (12).

Treg infiltration into the tumor microenvironment is facilitated by binding of the chemokine receptor CCR4, expressed on Tregs, to its ligand CCL22, which is secreted by many types of tumor cells. While the differentiation and expansion of Tregs is induced by TGF-β (12).

Regarding autoimmune diseases, high FOXP3 expression was correlated with disease activity in autoimmune diseases including lupus nephritis (13), oral lichen planus (14), and in synovial fluid for patients with active rheumatoid arthritis (15).

A decrease in the number of Tregs in the peripheral blood of patients following organ transplantation correlates with decreased graft survival (16).

While graft survival following kidney transplant recipients was also improved in patients who maintained Treg levels one year after transplantation, other studies have shown conflicting findings (17).

These studies highlight the promising role of immunohistochemical evaluation of FOXP3 as a routine affordable marker in predicting disease activity of autoimmune diseases and as a prognostic marker for various types of

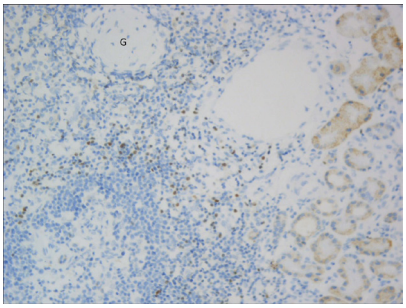

Figure 1. A case of proliferative lupus nephritis class IV with nuclear Foxp3 expression in <11%-50% of cells (original magnification ×200) (18).

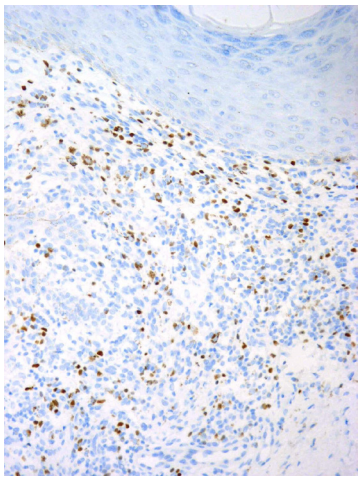

Figure 2. A case of oral lichen planus showing high expression of FOXP3 positive Treg cells in dermis (original magnification ×200).

carcinoma.

The appearance of FOXP3 expression by immunohistochemistry and flow cytometry is illustrated in Figures 1 (18), 2 and 3.

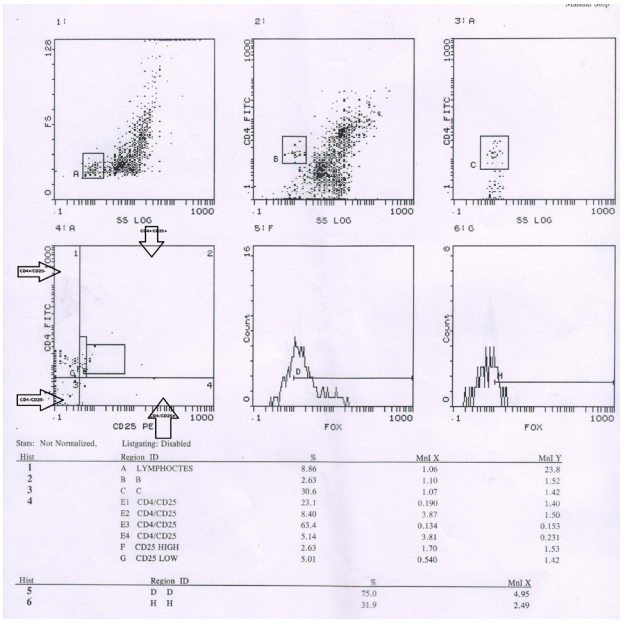

Figure 3. CD4-CD25-FOXP3 expression by flowcytometry in colorectal cancer patients.
A: percent of lymphocytes; E: CD4+/CD25+ percentage; F: CD25 high; D: FOX expression on CD25.

Conflicts of interest

None to be declared.

Authors' contribution

Marwa M Shakweer and Nadia M El-Sheshtawy wrote the manuscript equally.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006; 441:235-8.
2. Curiel TJ. Tregs and rethinking cancer immunotherapy. J Clin Invest. 2007;117:1167-74.
3. Chen W. Tregs in immunotherapy: opportunities and challenges. Immunotherapy. 2011; 3:911-4.
4. Fontenot JD, Rasmussen JP, Williams LM, Dooley JL, Farr AG, Rudensky AY. Regulatory T cell lineage specification by the forkhead transcription factor foxp3. Immunity. 2005; 22:329-41.
5. Takahashi T, Kuniyasu Y, Toda M, Sakaguchi N, Itoh M, Iwata M, et al. Immunologic self-tolerance maintained by CD25+CD4+ naturally anergic and suppressive T cells: induction of autoimmune disease by breaking their anergic/suppressive state. Int Immunol. 1998;10:1969-80.
6. Adeegbe DO, Nishikawa H. Natural and induced T regulatory cells in cancer. Front Immunol. 2013;4:190.
7. Gooden MJ, de Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. Br J Cancer. 2011;105:93-103.
8. Oleinika K1, Nibbs RJ, Graham GJ, Fraser AR. Suppression, subversion and escape: the role of regulatory T cells in cancer progression. Clin Exp Immunol. 2013;171:36-45.
9. Curiel TJ. Regulatory T cells and treatment of cancer. Curr Opin Immunol. 2008;20:241-6.
10. Wolf D, Wolf AM, Rumpold H, Fiegl H, Zeimet AG, Muller-Holzner E, et al. The expression of the regulatory T cell–specific forkhead box transcription factor FoxP3 is associated with poor prognosis in ovarian cancer. Clin Cancer Res. 2005; 11:8326-31.
11. Petersen RP, Campa MJ, Sperlazza J, Conlon D, Joshi MB, Harpole DH, et al. Tumor infiltrating Foxp3+ regulatory T-cells are associated with recurrence in pathologic stage I NSCLC patients. Cancer. 2006;107:2866-72.
12. Lippitz BE. Cytokine patterns in patients with cancer: a systematic review. Lancet Oncol. 2013;14:e218-28.
13. Wang G, Lai FM, Tam LS, Li EK, Kwan BC, Chow KM, et al. Urinary FOXP3 mRNA in patients with lupus nephritis--relation with disease activity and treatment response. Rheumatology (Oxford). 2009;48:755-60.
14. Tao XA, Xia J, Chen XB, Wang H, Dai YH, Rhodus NL, et al. FOXP3+ T regulatory cells in lesions of oral lichen planus correlated with disease activity. Oral Dis. 2010;16:76-82.
15. Jiao Z, Wang W, Jia R, Li J, You H, Chen L, et al. Accumulation of FoxP3-expressing CD4+ CD25+ T cells with distinct chemokine receptors in synovial fluid of patients with active

rheumatoid arthritis. Scand J Rheumatol. 2007;36:428-33.
16. Vallotton L, Hadaya K, Venetz JP, Buehler LH, Ciuffreda D, Nseir G, et al. Monitoring of CD4+CD25highIL-7Rαhigh activated T cells in kidney transplant recipients. Clin J Am Soc Nephrol. 2011;6:2025-33.
17. San Segundo D, Fernández-Fresnedo G, Rodrigo E, Ruiz JC, González M, Gómez-Alamillo C, et al. High regulatory T-cell levels at 1 year posttransplantation predict long-term graft survival among kidney transplant recipients. Transplant Proc. 2012; 44:2538-41.
18. Shakweer MM, Behairy M, Elhefnawy NG, Elsaid TW. Value of Foxp3 expressing T-regulatory cells in renal tissue in lupus nephritis; an immunohistochemical study. J Nephropathol. 2016;5:105-110.