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# Deep Insight Section

# FOXP3 expression in tumor cells and its role in cancer progression

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## Abstract

Forkhead box P3 (FOXP3), a gene member of the forkhead/winged-helix family of transcription regulators, is implicated in regulating immune system development and function. This gene has been found to be of crucial importance for the generation of $CD4^+CD25^+$ regulatory T cells (Tregs). In addition to its expression in the lymphocyte lineage, studies have recently described FOXP3 expression in normal and cancer cells non-hematopoietic-derived, suggesting that FOXP3 exerts a broader function than that on Tregs.
A role for FOXP3 as an onco-suppressor gene in human cancers has been suggested based on *in vitro* studies showing that FOXP3 is implicated in repressing various oncogenes and enhancing expression of tumor-suppressor genes. However, numerous studies in samples from human cancer patients showed a positive correlation between FOXP3 expression and poor prognosis, especially with metastasis.
Further investigations are required to clarify the significance of FOXP3 expression in tumor cells and to identify the mechanisms by which it affects prognosis.

## Introduction

Forkhead box P3 (FOXP3) is a member of the forkhead/winged-helix family of transcription regulators. This gene is involved in immune system responses and in the development and function of regulatory T cells (Tregs) (Fontenot et al., 2005; Sakaguchi et al., 2008). The FOXP3 gene is located on the X chromosome at Xp11.23 and it is submitted to X chromosome inactivation (Wang et al., 2009). This gene is highly conserved across mammals (Ziegler, 2006) and contains 11 coding exons and 3 non-coding exons (Bennett and Ochs, 2001). FOXP3 protein contains four potential functional domains; repressor, zinc finger, leucine zipper and forkhead. Humans express both full-length protein and three splice variants (Allan et al., 2005; Kaur et al., 2010; Smith et al., 2006). The full-lenght form consists of 431-amino acids with a molecular weight of 47 kDa. The isoform Δ2FOXP3, lacking exon 2 (aa 71-105), has been proposed to act as a dominant negative isoform (Li et al., 2007). Another splice variant of FOXP3, called Δ7FOXP3, has been identified in both $CD4^+$ and $CD8^+$ regulatory T cell clones. Δ7FOXP3 lacks the 81 bp region that encodes exon 7. The absence of this exon abrogates the suppressive function of Tregs (Kaur et al., 2010). Human Tregs can also express Δ2Δ7FOXP3 isoform that lacks both exon 2 and exon 7 (aa 245-272) (Mailer et al., 2009).

## FOXP3 expression in regulatory T cells

The nuclear expression of FOXP3 is considered as the most specific marker for Tregs and a key determinant of their immunosuppressive functions (Grimmig et al., 2013). The molecular mechanisms of Treg-mediated immunosuppression are still not

completely understood. Genome-wide analyses of FOXP3$^+$ T cells revealed about 700 genes and many microRNAs differentially expressed in FOXP3$^+$ Tregs. In these cells FOXP3 has a dual role as both transcriptional activator and repressor (Sadlon et al., 2010; Zheng et al., 2007).

Regulatory T cells represent about 5% of circulating CD4$^+$ T lymphocytes in the human peripheral blood. An increased number of Tregs has been observed in the blood, in the tumor mass and in the draining lymph nodes of patients with different solid tumors (Bergmann et al., 2008; Mougiakakos et al., 2010; Petersen et al., 2006; Strauss et al., 2007; Whiteside, 2012). The increased frequency of tumor-infiltrating Tregs have been associated with poor survival in breast (Bates et al., 2006), gastric (Sasada et al., 2003), ovarian (Sato et al., 2005), lung (Petersen et al., 2006), hepatocellular (Gao et al., 2007), renal (Li et al., 2009), and pancreatic (Hiraoka et al., 2006) cancers.

After migrating to tumor site, Tregs suppress antitumor immune response interfering with the activation and expansion of tumor-antigens-specific effector T cells through different mechanisms not fully understood yet (Whiteside, 2008).

In breast cancer, the percentage of Treg cells increases in parallel with the disease stage, from normal to ductal carcinoma in situ (DCIS) and from DCIS to invasive carcinoma. A high frequency of tumor-infiltrating FOXP3$^+$ cells correlates with worse disease-free survival and decreased overall survival in patients with invasive breast carcinoma, suggesting that the presence of Treg cells promotes tumour progression by creating an immunosuppressive environment (Bates et al., 2006).

Tan and colleagues proposed a further explanation for the association of Treg cells with an aggressive phenotype in advanced breast cancers by demonstrating that tumor-infiltrating FOXP3$^+$ Tregs are responsible for high RANKL expression within the tumor microenvironment, and this expression stimulates the metastatic progression of RANK-expressing breast carcinoma cells (Tan et al., 2011).

Tregs are also directly involved in promoting angiogenesis in the tumor microenvironment (Facciabene et al., 2012), therefore Tregs might promote cancer growth both through tumor immune escape and angiogenesis.

In addition to their potential role in favoring disease progression and relapse, FOXP3$^+$ Tregs have been suggested as possible biomarker to monitor the therapeutic response. For example, it has been observed that the decrease of FOXP3$^+$ tumor-infiltrating cells is associated with the pathological complete response in breast cancer patients submitted to neoadiuvant chemotherapy (Ladoire et al., 2008).

Contrary to the putative pro-tumorigenic effect, the presence of Tregs has been associated with a good prognosis in colorectal and head and neck cancers (Badoual et al., 2006; Ladoire et al., 2011). Although Tregs can potentially promote cancer progression, they can also attenuate inflammation. Because chronic inflammation is one of the critical processes promoting carcinogenesis and tumor growth, Tregs are able to down-regulate the pro-tumorigenic inflammatory responses. It has been hypothesized that colorectal cancer growth can be promoted by a Th17-cell mediated inflammatory response. Human Tregs are able to limit Th17-related pro-tumorigenic effects through inhibition of their activation and function (Crome et al., 2010).

## FOXP3 expression in malignant cells

FOXP3 expression has been recently described in normal cells and in non-hematopoietic-derived cancer cells, suggesting that FOXP3 biological effects are not restricted to Tregs. FOXP3 expression has been observed in different cancer histotypes (breast, urinary bladder, tongue, gastric, esophageal, pancreas, colorectal, stomach, thyroid, glioma, non-small cell lung cancers and melanoma). Studies performed on samples from human cancer patients have produced data showing FOXP3 expression restricted only to cancer cells, whereas weak or no FOXP3 expression was detectable in their respective normal counterpart (Ebert et al., 2008; Fu et al., 2013; Hinz et al., 2007; Wang et al., 2012; Wang et al., 2014; Won et al., 2013).

In contrast, Zuo and colleagues reported a higher expression of FOXP3 in normal epithelial breast cells than in tumor cells (Zuo et al., 2007b). Similar findings have been reported in samples of prostate and ovarian cancer, where FOXP3 protein was clearly identifiable in normal epithelial samples, while the majority of malignant cells resulted negative for this protein (Wang et al., 2009; Zhang and Sun, 2010).

To note in most carcinomas, FOXP3 staining was localized predominantly in the cytoplasm of tumor cells, whereas in the studies by Zuo and Wang only nuclear positivity for FOXP3 was scored as a positive result (Wang et al., 2009; Zuo et al., 2007b).

## Tumor suppressive role of FOXP3

*In vitro* studies demonstrated an important role of FOXP3 modulating the expression of various genes

implicated in cancer development, including tumor suppressors and oncogenes.
For instance, FOXP3 represses the expression of HER2 and SKP2 in breast cancer cells (Zuo et al., 2007a; Zuo et al., 2007b) and an inverse correlation between FOXP3 and HER2 mRNA was observed in this type of tumor. Similarly, FOXP3 silencing in normal mammary epithelial cells (where FOXP3 is expressed at higher level compared to tumor tissue) determines an increase in HER2 expression (Zuo et al., 2007b). FOXP3 can also down-regulate BRCA1, interfering with the BRCA1-mediated DNA repair processes (Li et al., 2013).
Moreover, FOXP3 is involved in the transcriptional control of tumor-suppressor genes such as p21 and LATS2 (Li et al., 2011). In prostate cancer, FOXP3 is also able to repress the expression of c-Myc whose overexpression contributes to a more aggressive cancer phenotype (Wang et al., 2009).
FOXP3 has been demonstrated to play a tumor-suppressor role also in gastric cancer cells. In these cells the up-regulation of FOXP3 expression significantly inhibit cell growth and promote apoptosis, through the induction of pro-apoptotic genes (PARP, caspase-3 and caspase-9), suggesting that endogenous FOXP3 might act as a positive modulator in apoptotic pathway (Ma et al., 2013). Furthermore, in gastric cancer as in other malignancies, COX-2 has been shown to play an important role in both carcinogenesis and cancer progression. By inhibiting NF-κB activity, which is a major modulator of COX-2 expression, FOXP3 inhibits the expression of COX2 and hence cell metastasis (Hao et al., 2014).

## FOXP3 expression and prognosis in human cancer

Although FOXP3 has been described as an onco-suppressor gene, recent evidences point out the positive correlation between FOXP3 expression and poor prognosis.
In 2009, Merlo and colleagues demonstrated, for the first time, that FOXP3 expression in breast carcinoma was inversely associated with patient survival and that the risk increased with FOXP3 staining intensity. FOXP3 was also a strong prognostic factor for distant metastasis-free survival, but not for local recurrence incidence risk (Merlo et al., 2009). These results were confirmed by other 2 independent studies (Kim MH et al., 2013; Nair et al., 2013).
The frequency of FOXP3 positive cancer cells in primary gastric tumors correlated with the incidence of lymph node metastases (Yoshii et al., 2012; Wang et al., 2010) and the 3-year survival rate, indicating a potential association of FOXP3 expression with poor prognosis. In this regard, it has been demonstrated that gastric carcinoma cells might have a Treg-like activity, which would allow them to escape from immune surveillance, thereby resulting in cancer progression (Yoshii et al., 2012).
A correlation between FOXP3 expression and lymph node metastases incidence was also reported for esophageal squamous carcinoma (Xue et al., 2010), where FOXP3 mRNA and protein expression was not only higher in tumors than in normal mucosa, but also higher in advanced stages than in early stages. FOXP3 negative patients experienced significantly better overall survival than the FOXP3-overexpressing group. Cox regression analysis showed that tumor stage and FOXP3 protein expression were independent prognostic risk factors (Wang et al., 2012).
Two different studies on non-small-cell lung cancer patients demonstrated that FOXP3 expression in cancer cells positively correlated with both lymph node metastases and tumor staging (Dimitrakopoulos et al., 2011; Fu et al., 2013).
FOXP3 expression has been correlated with poor prognosis even in colorectal (Kim M et al., 2013), tongue (Liang et al., 2011), urinary bladder (Winerdal et al., 2011) cancer patients, and glioma (Wang et al., 2014) patients.
Finally, *in vitro* studies demonstrated that FOXP3 expression in tumor cells correlates with the inhibition of T-cell proliferation, indicating that FOXP3-positive cancer cells may acquire growth-suppressive functions, similar to Tregs, and that mimicking Tregs functions may represent a novel mechanism of immune evasion (Grimmig et al., 2013; Hinz et al., 2007).
All this data highlights the association between FOXP3 expression in tumor cells and poor patient prognosis. Notably, FOXP3 has not been associated with local recurrence but only with a possible role in driving metastatic spread.

## FOXP3 localization in cancer cells and patient prognosis

FOXP3 protein is synthesized in the cytoplasm of cells and then actively transported to the nucleus. As a transcription factor, the nuclear localization is required for its transcriptional repression function (Lopes et al., 2006).
FOXP3 is expressed constitutively within the nucleus of Tregs and of those normal FOXP3-expressing epithelial cells (Sakaguchi, 2005). By contrast, several studies demonstrated that FOXP3 cytoplasmic staining was more aboundant, compared to nuclear expression, in several types of cancer (Hinz et al., 2007; Karanikas et al., 2008; Ladoire et al., 2011; Merlo et al., 2009; Tao et al., 2012; Winerdal et al., 2011).
The fact that many tumors display cytoplasmic staining may be a result of defects in the nuclear localization signals of FOXP3, possibly due to acquired mutations. Frequent FOXP3 gene mutations and deletions, together with post-

translational modifications and splicing variations may result in cytoplasmic localization of FOXP3 protein in cancer cells (Wang et al., 2009; Hancock and Ozkaynak, 2009). Since the role of FOXP3 is transcription regulation, a cytoplasmic FOXP3 localization could affect its biological role. The concept that FOXP3 cytoplasmic localization interferes with its onco-suppressive functions has been suggested by a recent study (Takenaka et al., 2013). Nuclear FOXP3 expression has been associated significantly with an improved overall survival in breast cancer patients, whereas cytoplasmic FOXP3 expression in tumor cells was significantly associated with poor clinical outcome (Takenaka et al., 2013). A predominant cytoplasmic FOXP3 localization has also been described in melanoma and colorectal cancer, where FOXP3 expression correlated with poor prognosis (Kim et al., 2013; Quaglino et al., 2011).

In contrast with these findings cytoplasmic FOXP3 expression was associated with better overall survival and disease-free survival in primary invasive HER2-overexpressing breast cancer patients (Ladoire et al., 2011).

## Conclusions

Since Treg cells are significant mediators of tumor progression, targeting Tregs is under active investigation. Many studies have already demonstrated that Tregs depletion is a promising way to promote antitumor immunity and tumor regression (Jarry et al., 2014; Keenan et al., 2014; Reginato et al., 2013; Zhou et al., 2013).

In contrast, despite the increasing knowledge about the biology of FOXP3, the prognostic value of its expression in human cancer cells remains still controversial. The mechanism by which FOXP3 expression in tumor cells affects prognosis has not been fully elucidated yet. However, immune evasion, via FOXP3 expression in tumor cells, may represent the main strategy for cancer progression.

Further investigations are needed to clarify the significance of FOXP3 expression, its regulatory mechanism and its association with prognosis of human cancer. Moreover, additional studies should be carried out to clarify whether FOXP3 sub-cellular localization in tumor cells could be functionally relevant to the clinical prognosis.

# References

Bennett CL, Ochs HD. IPEX is a unique X-linked syndrome characterized by immune dysfunction, polyendocrinopathy, enteropathy, and a variety of autoimmune phenomena. Curr Opin Pediatr. 2001 Dec;13(6):533-8

Sasada T, Kimura M, Yoshida Y, Kanai M, Takabayashi A. CD4+CD25+ regulatory T cells in patients with gastrointestinal malignancies: possible involvement of regulatory T cells in disease progression. Cancer. 2003 Sep 1;98(5):1089-99

Allan SE, Passerini L, Bacchetta R, Crellin N, Dai M, Orban PC, Ziegler SF, Roncarolo MG, Levings MK. The role of 2 FOXP3 isoforms in the generation of human CD4+ Tregs. J Clin Invest. 2005 Nov;115(11):3276-84

Fontenot JD, Rasmussen JP, Gavin MA, Rudensky AY. A function for interleukin 2 in Foxp3-expressing regulatory T cells. Nat Immunol. 2005 Nov;6(11):1142-51

Sakaguchi S. Naturally arising Foxp3-expressing CD25+CD4+ regulatory T cells in immunological tolerance to self and non-self. Nat Immunol. 2005 Apr;6(4):345-52

Sato E, Olson SH, Ahn J, Bundy B, Nishikawa H, Qian F, Jungbluth AA, Frosina D, Gnjatic S, Ambrosone C, Kepner J, Odunsi T, Ritter G, Lele S, Chen YT, Ohtani H, Old LJ, Odunsi K. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. Proc Natl Acad Sci U S A. 2005 Dec 20;102(51):18538-43

Badoual C, Hans S, Rodriguez J, Peyrard S, Klein C, Agueznay Nel H, Mosseri V, Laccourreye O, Bruneval P, Fridman WH, Brasnu DF, Tartour E. Prognostic value of tumor-infiltrating CD4+ T-cell subpopulations in head and neck cancers. Clin Cancer Res. 2006 Jan 15;12(2):465-72

Bates GJ, Fox SB, Han C, Leek RD, Garcia JF, Harris AL, Banham AH. Quantification of regulatory T cells enables the identification of high-risk breast cancer patients and those at risk of late relapse. J Clin Oncol. 2006 Dec 1;24(34):5373-80

Hiraoka N, Onozato K, Kosuge T, Hirohashi S. Prevalence of FOXP3+ regulatory T cells increases during the progression of pancreatic ductal adenocarcinoma and its premalignant lesions. Clin Cancer Res. 2006 Sep 15;12(18):5423-34

Lopes JE, Torgerson TR, Schubert LA, Anover SD, Ocheltree EL, Ochs HD, Ziegler SF. Analysis of FOXP3 reveals multiple domains required for its function as a transcriptional repressor. J Immunol. 2006 Sep 1;177(5):3133-42

Petersen RP, Campa MJ, Sperlazza J, Conlon D, Joshi MB, Harpole DH Jr, Patz EF Jr. Tumor infiltrating Foxp3+ regulatory T-cells are associated with recurrence in pathologic stage I NSCLC patients. Cancer. 2006 Dec 15;107(12):2866-72

Smith EL, Finney HM, Nesbitt AM, Ramsdell F, Robinson MK. Splice variants of human FOXP3 are functional inhibitors of human CD4+ T-cell activation. Immunology. 2006 Oct;119(2):203-11

Ziegler SF. FOXP3: of mice and men. Annu Rev Immunol. 2006;24:209-26

Gao Q, Qiu SJ, Fan J, Zhou J, Wang XY, Xiao YS, Xu Y, Li YW, Tang ZY. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. J Clin Oncol. 2007 Jun 20;25(18):2586-93

Hinz S, Pagerols-Raluy L, Oberg HH, Ammerpohl O, Grüssel S, Sipos B, Grützmann R, Pilarsky C, Ungefroren H, Saeger HD, Klöppel G, Kabelitz D, Kalthoff H. Foxp3 expression in pancreatic carcinoma cells as a novel mechanism of immune evasion in cancer. Cancer Res. 2007 Sep 1;67(17):8344-50

Li B, Samanta A, Song X, Iacono KT, Bembas K, Tao R, Basu S, Riley JL, Hancock WW, Shen Y, Saouaf SJ, Greene MI. FOXP3 interactions with histone acetyltransferase and class II histone deacetylases are required for repression. Proc Natl Acad Sci U S A. 2007 Mar 13;104(11):4571-6

Strauss L, Bergmann C, Gooding W, Johnson JT, Whiteside TL. The frequency and suppressor function of CD4+CD25highFoxp3+ T cells in the circulation of patients with squamous cell carcinoma of the head and neck. Clin Cancer Res. 2007 Nov 1;13(21):6301-11

Zheng Y, Josefowicz SZ, Kas A, Chu TT, Gavin MA, Rudensky AY. Genome-wide analysis of Foxp3 target genes in developing and mature regulatory T cells. Nature. 2007 Feb 22;445(7130):936-40

Zuo T, Liu R, Zhang H, Chang X, Liu Y, Wang L, Zheng P, Liu Y. FOXP3 is a novel transcriptional repressor for the breast cancer oncogene SKP2. J Clin Invest. 2007a Dec;117(12):3765-73

Zuo T, Wang L, Morrison C, Chang X, Zhang H, Li W, Liu Y, Wang Y, Liu X, Chan MW, Liu JQ, Love R, Liu CG, Godfrey V, Shen R, Huang TH, Yang T, Park BK, Wang CY, Zheng P, Liu Y. FOXP3 is an X-linked breast cancer suppressor gene and an important repressor of the HER-2/ErbB2 oncogene. Cell. 2007b Jun 29;129(7):1275-86

Bergmann C, Strauss L, Wang Y, Szczepanski MJ, Lang S, Johnson JT, Whiteside TL. T regulatory type 1 cells in squamous cell carcinoma of the head and neck: mechanisms of suppression and expansion in advanced disease. Clin Cancer Res. 2008 Jun 15;14(12):3706-15

Ebert LM, Tan BS, Browning J, Svobodova S, Russell SE, Kirkpatrick N, Gedye C, Moss D, Ng SP, MacGregor D, Davis ID, Cebon J, Chen W. The regulatory T cell-associated transcription factor FoxP3 is expressed by tumor cells. Cancer Res. 2008 Apr 15;68(8):3001-9

Karanikas V, Speletas M, Zamanakou M, Kalala F, Loules G, Kerenidi T, Barda AK, Gourgoulianis KI, Germenis AE. Foxp3 expression in human cancer cells. J Transl Med. 2008 Apr 22;6:19

Ladoire S, Arnould L, Apetoh L, Coudert B, Martin F, Chauffert B, Fumoleau P, Ghiringhelli F. Pathologic complete response to neoadjuvant chemotherapy of breast carcinoma is associated with the disappearance of tumor-infiltrating foxp3+ regulatory T cells. Clin Cancer Res. 2008 Apr 15;14(8):2413-20

Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. Cell. 2008 May 30;133(5):775-87

Whiteside TL. The tumor microenvironment and its role in promoting tumor growth. Oncogene. 2008 Oct 6;27(45):5904-12

Hancock WW, Ozkaynak E. Three distinct domains contribute to nuclear transport of murine Foxp3. PLoS One. 2009 Nov 18;4(11):e7890

Li JF, Chu YW, Wang GM, Zhu TY, Rong RM, Hou J, Xu M. The prognostic value of peritumoral regulatory T cells and its correlation with intratumoral cyclooxygenase-2 expression in clear cell renal cell carcinoma. BJU Int. 2009 Feb;103(3):399-405

Mailer RK, Falk K, Rötzschke O. Absence of leucine zipper in the natural FOXP3Delta2Delta7 isoform does not affect dimerization but abrogates suppressive capacity. PLoS One. 2009 Jul 1;4(7):e6104

Merlo A, Casalini P, Carcangiu ML, Malventano C, Triulzi T, Mènard S, Tagliabue E, Balsari A. FOXP3 expression and overall survival in breast cancer. J Clin Oncol. 2009 Apr 10;27(11):1746-52

Wang L, Liu R, Li W, Chen C, Katoh H, Chen GY, McNally B, Lin L, Zhou P, Zuo T, Cooney KA, Liu Y, Zheng P. Somatic single hits inactivate the X-linked tumor suppressor FOXP3 in the prostate. Cancer Cell. 2009 Oct 6;16(4):336-46

Crome SQ, Clive B, Wang AY, Kang CY, Chow V, Yu J, Lai A, Ghahary A, Broady R, Levings MK. Inflammatory effects of ex vivo human Th17 cells are suppressed by regulatory T cells. J Immunol. 2010 Sep 15;185(6):3199-208

Kaur G, Goodall JC, Jarvis LB, Hill Gaston JS. Characterisation of Foxp3 splice variants in human CD4+

and CD8+ T cells--identification of Foxp3Δ7 in human regulatory T cells. Mol Immunol. 2010 Nov-Dec;48(1-3):321-32

Mougiakakos D, Choudhury A, Lladser A, Kiessling R, Johansson CC. Regulatory T cells in cancer. Adv Cancer Res. 2010;107:57-117

Sadlon TJ, Wilkinson BG, Pederson S, Brown CY, Bresatz S, Gargett T, Melville EL, Peng K, D'Andrea RJ, Glonek GG, Goodall GJ, Zola H, Shannon MF, Barry SC. Genome-wide identification of human FOXP3 target genes in natural regulatory T cells. J Immunol. 2010 Jul 15;185(2):1071-81

Wang LH, Su L, Wang JT. Correlation between elevated FOXP3 expression and increased lymph node metastasis of gastric cancer. Chin Med J (Engl). 2010 Dec;123(24):3545-9

Xue L, Lu HQ, He J, Zhao XW, Zhong L, Zhang ZZ, Xu ZF. Expression of FOXP3 in esophageal squamous cell carcinoma relating to the clinical data. Dis Esophagus. 2010 May;23(4):340-6

Zhang HY, Sun H. Up-regulation of Foxp3 inhibits cell proliferation, migration and invasion in epithelial ovarian cancer. Cancer Lett. 2010 Jan 1;287(1):91-7

Dimitrakopoulos FI, Papadaki H, Antonacopoulou AG, Kottorou A, Gotsis AD, Scopa C, Kalofonos HP, Mouzaki A. Association of FOXP3 expression with non-small cell lung cancer. Anticancer Res. 2011 May;31(5):1677-83

Ladoire S, Martin F, Ghiringhelli F. Prognostic role of FOXP3+ regulatory T cells infiltrating human carcinomas: the paradox of colorectal cancer. Cancer Immunol Immunother. 2011 Jul;60(7):909-18

Li W, Wang L, Katoh H, Liu R, Zheng P, Liu Y. Identification of a tumor suppressor relay between the FOXP3 and the Hippo pathways in breast and prostate cancers. Cancer Res. 2011 Mar 15;71(6):2162-71

Liang YJ, Liu HC, Su YX, Zhang TH, Chu M, Liang LZ, Liao GQ. Foxp3 expressed by tongue squamous cell carcinoma cells correlates with clinicopathologic features and overall survival in tongue squamous cell carcinoma patients. Oral Oncol. 2011 Jul;47(7):566-70

Quaglino P, Osella-Abate S, Marenco F, Nardò T, Gado C, Novelli M, Savoia P, Bernengo MG. FoxP3 expression on melanoma cells is related to early visceral spreading in melanoma patients treated by electrochemotherapy. Pigment Cell Melanoma Res. 2011 Aug;24(4):734-6

Tan W, Zhang W, Strasner A, Grivennikov S, Cheng JQ, Hoffman RM, Karin M. Tumour-infiltrating regulatory T cells stimulate mammary cancer metastasis through RANKL-RANK signalling. Nature. 2011 Feb 24;470(7335):548-53

Winerdal ME, Marits P, Winerdal M, Hasan M, Rosenblatt R, Tolf A, Selling K, Sherif A, Winqvist O. FOXP3 and survival in urinary bladder cancer. BJU Int. 2011 Nov;108(10):1672-8

Facciabene A, Motz GT, Coukos G. T-regulatory cells: key players in tumor immune escape and angiogenesis. Cancer Res. 2012 May 1;72(9):2162-71

Tao H, Mimura Y, Aoe K, Kobayashi S, Yamamoto H, Matsuda E, Okabe K, Matsumoto T, Sugi K, Ueoka H. Prognostic potential of FOXP3 expression in non-small cell

lung cancer cells combined with tumor-infiltrating regulatory T cells. Lung Cancer. 2012 Jan;75(1):95-101

Wang G, Liu G, Liu Y, Li X, Su Z. FOXP3 expression in esophageal cancer cells is associated with poor prognosis in esophageal cancer. Hepatogastroenterology. 2012 Oct;59(119):2186-91

Whiteside TL. What are regulatory T cells (Treg) regulating in cancer and why? Semin Cancer Biol. 2012 Aug;22(4):327-34

Yoshii M, Tanaka H, Ohira M, Muguruma K, Iwauchi T, Lee T, Sakurai K, Kubo N, Yashiro M, Sawada T, Hirakawa K. Expression of Forkhead box P3 in tumour cells causes immunoregulatory function of signet ring cell carcinoma of the stomach. Br J Cancer. 2012 May 8;106(10):1668-74

Fu HY, Li C, Yang W, Gai XD, Jia T, Lei YM, Li Y. FOXP3 and TLR4 protein expression are correlated in non-small cell lung cancer: implications for tumor progression and escape. Acta Histochem. 2013 Mar;115(2):151-7

Grimmig T, Kim M, Germer CT, Gasser M, Waaga-Gasser AM. The role of FOXP3 in disease progression in colorectal cancer patients. Oncoimmunology. 2013 Jun 1;2(6):e24521

Kim M, Grimmig T, Grimm M, Lazariotou M, Meier E, Rosenwald A, Tsaur I, Blaheta R, Heemann U, Germer CT, Waaga-Gasser AM, Gasser M. Expression of Foxp3 in colorectal cancer but not in Treg cells correlates with disease progression in patients with colorectal cancer. PLoS One. 2013;8(1):e53630

Kim MH, Koo JS, Lee S. FOXP3 expression is related to high Ki-67 index and poor prognosis in lymph node-positive breast cancer patients. Oncology. 2013;85(2):128-36

Li W, Katoh H, Wang L, Yu X, Du Z, Yan X, Zheng P, Liu Y. FOXP3 regulates sensitivity of cancer cells to irradiation by transcriptional repression of BRCA1. Cancer Res. 2013 Apr 1;73(7):2170-80

Ma GF, Chen SY, Sun ZR, Miao Q, Liu YM, Zeng XQ, Luo TC, Ma LL, Lian JJ, Song DL. FoxP3 inhibits proliferation and induces apoptosis of gastric cancer cells by activating the apoptotic signaling pathway. Biochem Biophys Res Commun. 2013 Jan 11;430(2):804-9

Nair S, Aldrich AJ, McDonnell E, Cheng Q, Aggarwal A,

Patel P, Williams MM, Boczkowski D, Lyerly HK, Morse MA, Devi GR. Immunologic targeting of FOXP3 in inflammatory breast cancer cells. PLoS One. 2013;8(1):e53150

Reginato E, Mroz P, Chung H, Kawakubo M, Wolf P, Hamblin MR. Photodynamic therapy plus regulatory T-celldepletion produces immunity against a mouse tumour that expresses a self-antigen. Br J Cancer. 2013 Oct 15;109(8):2167-74

Takenaka M, Seki N, Toh U, Hattori S, Kawahara A, Yamaguchi T, Koura K, Takahashi R, Otsuka H, Takahashi H, Iwakuma N, Nakagawa S, Fujii T, Sasada T, Yamaguchi R, Yano H, Shirouzu K, Kage M. FOXP3 expression in tumor cells and tumor-infiltrating lymphocytes is associated with breast cancer prognosis. Mol Clin Oncol. 2013 Jul;1(4):625-632

Won KY, Kim HS, Sung JY, Kim GY, Lee J, Park YK, Kim YW, Suh JH, Lim SJ. Tumoral FOXP3 has potential oncogenic function in conjunction with the p53 tumor suppressor protein and infiltrated Tregs in human breast carcinomas. Pathol Res Pract. 2013 Dec;209(12):767-73

Zhou S, Chen L, Qin J, Li R, Tao H, Zhen Z, Chen H, Chen G, Yang Y, Liu B, She Z, Zhong C, Liang C. Depletion of CD4+ CD25+ regulatory T cells promotes CCL21-mediated antitumor immunity. PLoS One. 2013;8(9):e73952

Hao Q, Zhang C, Gao Y, Wang S, Li J, Li M, Xue X, Li W, Zhang W, Zhang Y. FOXP3 inhibits NF-κB activity and hence COX2 expression in gastric cancer cells. Cell Signal. 2014 Mar;26(3):564-9

Jarry U, Donnou S, Vincent M, Jeannin P, Pineau L, Fremaux I, Delneste Y, Couez D. Treg depletion followed by intracerebral CpG-ODN injection induce brain tumor rejection. J Neuroimmunol. 2014 Feb 15;267(1-2):35-42

Keenan BP, Saenger Y, Kafrouni MI, Leubner A, Lauer P, Maitra A, Rucki AA, Gunderson AJ, Coussens LM, Brockstedt DG, Dubensky TW Jr, Hassan R, Armstrong TD, Jaffee EM. A Listeria vaccine and depletion of T-regulatory cells activate immunity against early stage pancreatic intraepithelial neoplasms and prolong survival of mice. Gastroenterology. 2014 Jun;146(7):1784-94.e6

Wang L, Zhang B, Xu X, Zhang S, Yan X, Kong F, Feng X, Wang J. Clinical significance of FOXP3 expression in human gliomas. Clin Transl Oncol. 2014 Jan;16(1):36-43

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Uva V, Sfondrini L, Triulzi T, Casalini P, Tagliabue E, Balsari A. FOXP3 expression in tumor cells and its role in cancer progression. Atlas Genet Cytogenet Oncol Haematol. 2015; 19(3):234-239.