The global profile of histone H3 acetylation and methylation is affected by FOXP3

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Received January 12, 2016; Accepted June 8, 2016; Epub March 15, 2017; Published March 30, 2017

Abstract: As a regulator of Tregs and inflammation, the transcription factor forkhead/winged helix transcription factor 3 (FOXP3) plays important roles in some types of dermatitis. However, the detailed mechanism of FOXP3 has not been well defined. Increasing evidence indicates that FOXP3 involves epigenetic mechanisms to fulfill its functions. We anticipated several types of mechanisms that might link FOXP3 to the epigenetic profile, and assessed the impact of FOXP3 on the global profile of histone H3 acetylation and methylation. We found that overexpression of FOXP3 increased histone H3-lysine9 demethylation (H3K9me2), H3K79me2, H3-lysine9 acetylation (H3K9ac), and H3K18ac. When cells were exposed to ultraviolet (UV) light, FOXP3 clearly increased the levels of H3K9ac and H3K18ac. Hypoxia increased H3 modifications, whereas the overexpression of FOXP3 during hypoxia stabilized H3K9me2, H3K79me2, H3K9ac, and H3K18ac levels almost back to normal. FOXP3 functions opposite to TRAF6 (TNF receptor-associated factor 6) in H3 modifications. The modifications altered by FOXP3 may influence the cell cycle and apoptosis; we showed that FOXP3 increased the proportion of cells in S phase, decreased the proportion of cells in G2/M phase, and markedly enhanced cell apoptosis. In conclusion, this work provides evidence that FOXP3 is an epigenetic regulator, and implies a new molecular basis for the pathogenesis in some diseases.

Keywords: Acetylation, FOXP3 gene, histone modifications, methylation, psoriasis

Introduction

The transcription factor forkhead/winged helix transcription factor 3 (FOXP3) was initially identified as a key regulatory gene associated with the development and function of CD4+CD25+ regulatory T cells (Tregs) [1]. Tregs are crucial for the maintenance of immune homeostasis, self-tolerance, and tumor immune evasion/escape mainly because they suppress inflammation. Mutations and abnormalities in FOXP3 may cause a variety of autoimmune diseases, including IPEX (the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), defective of thymopoiesis, scurfy-like disease in humans [2-4] and homeostatic proliferation, allergic dysregulation, hyperimmunoglobulinemia E, and fatal lymphoproliferative disorder in mice [5-7].

FOXP3 also participates in many inflammatory dermatoses, including systemic lupus erythematosus [8, 9], atopic eczema [10], vitiligo [11, 12], idiopathic thrombocytopenic purpura [13], and especially psoriasis [14, 15]. Information regarding the functions of FOXP3 can therefore increase our understanding and ability to treat of these inflammatory dermatoses.

The signaling pathways governing FOXP3 transcription have been intensively studied [16]. FOXP3 functions as a transcription factor whereby it regulates the transcription of many target genes. Recent studies have suggested that post-translational modifications of histone maybe one of the main mechanisms by which FOXP3 fulfills its functions related to Tregs [17]. Our recent study showed that FOXP3 regulates the expression of Ezh2 methyltransferase [18]. In addition, it has been demonstrated that FOXP3 recruits and performs functions with the linker histone, histone deacetylases (TIP60), and class II histone acetyltransferases (HDAC7...
and HDAC9) [19]. These data suggest that manipulation of epigenetics “histone code” modifications maybe a downstream function of FOXP3 in the nucleus. However, until now, the histone H3 related global epigenetic modifications involving FOXP3 have not been well defined. Therefore, in this study, we analyzed global epigenetic modifications of histone H3 by FOXP3, and tried to explain the phenomenon related to the regulation mechanism of FOXP3.

Materials and methods

DNA plasmids and cell line

We amplified the FOXP3 gene from cDNA derived from human peripheral blood mononuclear cells. The PCR products were then cloned into the retrovirus vector pMigR1-GFP. TRAF6 was also amplified from cDNA derived from human peripheral blood mononuclear cells. The PCR products were then cloned into the retrovirus vector pCMV5. HEK 293T cells were transiently transfected either alone or in combination with these two vectors, using Lipofectamine 2000 (Invitrogen).

Western blot analysis

Protein samples from total cell lysates were separated by 10% SDS-PAGE and electrotransferred to PVDF membranes. The membranes were washed with TBST, blocked in 5% BSA for 1h, and then incubated with specific primary antibody at 4°C overnight. The primary antibodies were as follows. Methyl-Histone H3 Antibody Sampler Kit #9847, Acetyl-Histone H3 (Lys9) (C5B11) Rabbit mAb #9649, Acetyl-Histone H3 (Lys18) Antibody #9675, Acetyl-Histone H3 (Lys9/10) Antibody #9711, Phospho-Histone H3 (Ser10) (D2C8) XP® Rabbit mAb #3377, Acetyl-Histone H3 (Lys23) Antibody #8848(Cell Signaling Technology, USA), anti-FOXP3(Abcam, USA), and anti-tubulin (Sigma, USA). After that, the membranes were washed with TBST and incubated with secondary antibodies for 1 h at room temperature. Immunoreactive bands were visualized using a chemiluminescence detection system (GE Healthcare, USA).

Hypoxia and UV irradiation

For hypoxia treatment, cells were cultured in 0.2% O₂ and 5% CO₂ for 24 hours. Incubations were performed in an Inviv O₂ 400 glove box hypoxia workstation equipped with a Ruskinn hypoxia gas mixer (Ruskinn Technology, UK). For UV irradiation, cells were exposed at a low energy irradiation of 5 J/m² for 15 seconds.

Cell cycle and apoptosis

For cell cycle analysis, collected cells were washed with PBS and fixed in 70% ethanol overnight or for more than 12 h at 4°C. The cells were then resuspended in 0.5 mL PBS. PI (50 μg/ml), RNase A (100 μg/ml), and Triton X-100 (0.2%) were added and the cells were incubated for 30 minutes in the dark at 4°C. Flow cytometry (Beckman Coulter) was then performed. For cell apoptosis assays, cells were washed and incubated with Annexin-V-FLUOS reagent (Roche Applied Science, Germany) in HEPES buffer that contained PI or a similar cell surface labeling reagent. The samples were then analyzed using a flow cytometer.

Statistical analysis

Analysis for statistical differences was performed with Student’s t-test, using STATA statistical software (version 11.0, STATA Corp, College Station, TX, USA). P-values less than 0.05 were considered significant.

Results

Overexpression of FOXP3 changed the global profile of histone H3 modifications

We speculated that targeting the epigenetic modifications of histone H3 might be another approach by which FOXP3 fulfills its functions. In this section, the global changes in ten types of histone H3 modifications resulting from the overexpression of FOXP3 were investigated (see Figure 1). First, there’s a significant increase in global levels of histone H3-lysine9 demethylation (H3K9me2), H3K27me2, H3K79me2, H3K36me2, H3-lysine9 acetylation (H3K9ac), H3K18ac, the phosphorylation of histone H3 serine 10 (H3S10-p), and H3K9ac/S10-p. H3K4me2 and H3K23ac showed no obvious changes. In addition, silencing FOXP3 with shRNAs reversed these histone H3 post-translational modifications (data not shown). These results demonstrate a role for FOXP3 in modifying the global profile of histone H3 modifications. FOXP3 could have an impact on the pattern of histone H3 methylation, acetylation,
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and phosphorylation, mainly by increasing their levels. This evidence suggests a novel mechanism for FOXP3 to regulate its target genes.

**FOXP3 stabilized the global modifications of histone H3 under hypoxia**

Hypoxia and hypoxia inducible factors play significant roles in regulating the development, differentiation, and function of T cells during inflammation. Inflammatory lesions often become severely hypoxic [20]. Cells at the site of inflammatory lesions may also experience hypoxia. Therefore, we sought to determine whether FOXP3 can regulate the global modification profile of histone H3 under hypoxia conditions.

We investigated five histone H3 modifications that were significantly altered, as show in Figure 1 (H3K9ac, H3K18ac, H3K79me2, and H3K9ac/S10-p). The levels of all five modifications were increased in vehicle transfected cells, whereas they were relatively decreased in FOXP3-transfected cells under hypoxia (Figure 2). FOXP3 appeared to stabilize global levels of these modifications to almost normal, pre-hypoxia levels. Consistent with published results [21, 22], here we observed that hypoxia also increased the levels of H3 methylation and acetylation. Increasing the expression of FOXP3 antagonized the impact of hypoxia, and resulted in decreased levels of histone H3 modifications. This phenomenon demonstrates that FOXP3 performs intertwined roles at both the molecular and cellular levels under hypoxic conditions.

**UV irradiation reduced global levels of histone H3 modifications**

Ultraviolet light is used to treat various dermatoses. In psoriasis, phototherapy treatment using UV irradiation has a history of nearly 90 years [23]. Its relative safety, effectiveness and affordability for ordinary people, all make this method a widely used treatment [24]. UV irradiation effectively generates DNA damage at low energy (e.g. 5 J/m² in our study). We found that, in response to UV at this low energy, the levels of H3K9ac, H3K18ac, H3S10-p and
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Figure 3. Changes in the global modification profile of histone H3 were induced by FOXP3 in cells irradiated with UV. Cells were exposed at irradiation (5 J/m²) for 15 seconds, and then collected for WB. A and B. Showed the WB band and the corresponding gray value respectively. Under UV, global levels of H3K9ac, H3K18ac, H3S10-p and H3K9ac/S10-p were decreased. FOXP3-transfected cells showed relatively higher levels of H3K9ac and H3K18ac than the vector-transfected cells.

Figure 4. Changes in cell cycle and apoptosis were induced by FOXP3 in cells exposed to UV irradiation. A and B. Showed the proportion of G1, S and G2/M phase in histogram and bar graph respectively. UV reduced the proportion of G2/M phase cells, and increased the proportion of G1 and S phase cells. FOXP3 increased the proportion of S phase cells and decreased the proportion of G2/M phase cells. C and D. Showed the proportion of cell apoptosis in histogram and bar graph respectively. FOXP3 markedly enhanced apoptosis in 293T cells, whereas UV had a weaker impact on apoptosis.

H3K9ac/S10-p were decreased (Figure 3). The regulation of histone H3 acetylation appears to be one of the main mechanisms by which UV functions. The decreased level of H3-K9ac observed in response to UV in our study is consistent with another published study. In which the authors screened DNA damage-responsive histone modifications and found that H3K9ac was rapidly and reversibly reduced in response to DNA damage by hydroxyurea and phleomycin in human cells [25]. Although this demonstrates the inhibitory effect of UV, there were still relatively higher levels of H3K9ac and H3K18-ac in FOXP3 transfected cells. This suggests that FOXP3 up-regulates acetyltransferase or delays the deacetylase process in cells exposed to UV.

UV irradiation alters cell-mediated immune responses, cytokine expression, the cell cycle and apoptosis. We next analyzed changes in the cell cycle and apoptosis in cells with or without FOXP3 that were exposed to UV light (Figure 4). In this section, FOXP3 increased the proportion of S phase cells and decreased the proportion of G2/M phase cells in the groups not exposed to UV. When exposed to low-energy UV radiation, no obvious differences were observed between vehicle transfected and FOXP3 transfected cells. However, the G1-phase was largely arrested and the number of cells in the G2/M phase was decreased in both cells. This suggests that the impact of FOXP3 on the cell cycle by FOXP3 was weaker than the impact of UV. Similar tendencies were observed in the impact of FOXP3 on the regul...
When analyzing cell apoptosis, we found that FOXP3 markedly enhanced the rate of apoptosis. S phase arrest and the promotion of apoptosis appeared to be vital mechanisms involved in the effect of FOXP3 in inhibiting cell proliferation and clone transformation. Different from its impact on cell cycle, low energy UV had a relatively weaker impact than FOXP3 on cell apoptosis. The impact on cell apoptosis by low energy UV was merged with the impact of FOXP3. FOXP3-transfected cells displayed relatively high proportions of apoptotic cell whether the cells were exposed to UV or not. This change in the tendency of cells to undergo apoptosis was consistent with the change observed in histone modifications (H3K9ac and H3K18ac) by FOXP3. These results suggest that the modulation of histone mediated post-translational modifications (H3K9ac and H3K18ac) may underlie the mechanisms by which FOXP3 induces cell apoptosis, also a process that requires further investigation.

TRAF6 interfered with the impacts of FOXP3 on the global profile of histone H3 modifications

Tumor necrosis factor receptor-associated factor 6 (TRAF6) is a T cell-intrinsic negative regulator, which has important position in regulation of innate immune responses and the maintenance of immune homoeostasis [26]. TRAF6 can induce T cell anergy. The T cell specific deletion of TRAF6 leads to resistance in responder T cells to suppression by Tregs and subsequent results in multiorgan inflammatory disease [27]. TRAF6 appears to play an important role in the maintenance of Tregs, even of their precursors and in their early generation in the thymus. TRAF6 deficient Tregs exhibit a more rapid conversion into FOXP3 cells than wild type Tregs, and TRAF6 deficient thymocytes show decreased levels of FOXP3 [28, 29]. TRAF6 has been demonstrated to interact with signaling molecules, including IL-17, TRAF3IP2, and miRNA-146a, and to participate in the regulation of inflammatory dermatosis (e.g. psoriasis vulgaris or psoriatic arthritis) [30-34]. TRAF6 has also been shown to be critically involved in the regulation of T cell immune responses, but until now, the mechanism by which TRAF6 functions with FOXP3 has not been fully explored. Moreover, there is no evidence that TRAF6 is involved in post-translational modifications mediated by histone H3. In our work, we observed that TRAF6 has an impact on histone H3 modifications with or without FOXP3.

We were surprised to find that levels of H3K9ac, H3K18ac, H3K9me2, and H3K79me2 were all significantly reduced in TRAF6-FOXP3 transfected cells compared to cells transfected with TRAF6 alone (Figure 5). TRAF6 and FOXP3 appeared to have antagonistic effects on H3 modifications, indicating the opposing effects for FOXP3 and TRAF6 in H3 modifications.

Under low-energy UV radiation, the global levels of H3K9ac, H3K18ac, H3K9me2 and H3K79me2 were markedly reduced in TRAF6-FOXP3 transfected cells, although these changes were not as clear as in TRAF6-FOXP3 transfected cells. The levels of these modifications were therefore relatively increased in TRAF6-FOXP3 transfected cells. We hypothesized that there may be mechanisms by which FOXP3 stabilizes the

Figure 5. Changes in the global modification profile of histone H3 were induced by TRAF6-FOXP3 transfection in cells exposed to UV irradiation or hypoxia. TRAF6-FOXP3 over-expressing cells were first transfected with the pCMV5-TRAF6 vector and later with the pMigR1-FOXP3 vector. A and B. Showed the WB band and the corresponding gray value respectively. The levels of H3K9ac, H3K18ac, H3K9me2 and H3K79me2 were all significantly reduced in TRAF6-FOXP3 transfected cells under normal conditions and when cells were exposed to UV, compared to cells transfected with TRAF6 alone. Under hypoxic condition, H3K9ac, H3K18ac, H3K9me2 and H3K79me2 were increased in TRAF6-FOXP3 transfected cells.
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H3 modifications in cells exposed to UV radiation.

We also investigated the global levels of four types of modifications under hypoxic conditions (Figure 5). There was a dramatic increase in the global levels of H3K9ac, H3K18ac, H3K9me2, and H3K79me2 in TRAF6-FOXP3 transfected cells, higher than those observed in TRAF6 transfected cells. Interestingly, these data are contrary to the observed decreased levels of these modifications in cells not exposed to hypoxia. The interplay among TRAF6, FOXP3, and hypoxia changed the levels of several types of H3 modifications. The complex mechanisms involved in this phenomenon require further study.

Overall, FOXP3 significantly altered the patterns of global H3 modifications induced by TRAF6, so that TRAF6-FOXP3 co-transfected cells behaved quite differently than cells transfected with TRAF6 alone. When no treatments were applied, over-expression of FOXP3 in cells made to pre-express TRAF6 decreased the profile of global H3 modifications. When exposed to UV radiation, cells over expressing FOXP3 also displayed decreased global levels of H3K9ac, H3K18ac and H3K79me2. Under hypoxic conditions, TRAF6-FOXP3 transfected cells displayed prominent up-regulation of H3K9ac, H3K18ac, H3K9me2 and H3K79me2. The mechanism by which TRAF6 and FOXP3 interacted to regulate the global levels of H3 modifications requires further investigation.

Our analysis of cell cycles demonstrated that FOXP3 had no obvious impacts on TRAF6 (Figure 6). Under hypoxic conditions, we observed G1 arrest that was accompanied by a decreased proportion of cells in the G2/M phase. There appeared little difference in cell cycle between TRAF6-FOXP3 transfected (S+G2/M phase = 23%) cells and cells transfected with TRAF6 alone (S+G2/M phase = 27%) under hypoxia. This suggests that the impact on the cell cycle by FOXP3 was weaker than the impact of hypoxia was.

In our study, both FOXP3 and hypoxia induced apoptosis. Compared to TRAF6 transfected cells, TRAF6-FOXP3 co-transfected cells exhibited a higher ratio of cells undergoing apoptosis whether the cells were exposed to hypoxia or not (Figure 6).

Discussion

Tregs play key regulatory roles in suppressing inflammation. As a master regulator of Tregs, the transcription factor FOXP3 has critical functions in many inflammatory diseases, such as psoriasis. Psoriasis is a chronic auto-inflammatory disorder of the skin. Recent findings have
suggested that epigenetic mechanisms, including DNA methylation, histone modifications, and microRNAs may be involved in this disease [35-37], but the precise molecular events involved in these epigenetic modifications are still not well understood.

Our previous studies revealed a defect in the nuclear localization of FOXP3 in psoriatic Tregs that was accompanied by a decreased in its ability to suppress pathogenic effector T cells [38]. These results suggested that a dysfunction involving FOXP3 might also have impact on psoriasis. FOXP3 also inhibited the activity of histone acetyltransferase inhibitor HDAC1 to modulate gene expression [39]. Moreover, it was reported that FOXP3 increased both H4K16 acetylation and H3K4 trimethylation, resulting in the activation of multiple genes [40]. Currently, the histone modification profiles affected by FOXP3, which may be tightly associated with gene expression patterns, have not been fully investigated. Analyzing the global epigenetic modification profile of histone H3 and how it is affected by FOXP3 may help us to learn how FOXP3 engages in the regulation of genes and the pathogenesis of dermatosis associated with autoimmune disorders.

As predicted, FOXP3 altered epigenetic modifications in this study. The levels of H3K9me2, H3K79me2, H3K36me2, H3K9ac, H3K18ac, H3S10-p and H3K9ac/S10-p were up-regulated. H3K9me2 has been correlated with chromatin condensing and is considered a prominent marker of transcriptional repression [41, 42]. H3K36m2 and H3K79m2 are often associated with transcriptional activation, and H3K79m2 is cell cycle dependent [43, 44]. Generally, histone acetylation, including H3K9ac and H3K18ac, is related to transcriptional activation [45, 46]. H3K9ac plays a role in eliciting immune responses [47]. H3S10-p is mainly correlated with chromosome condensation and gene regulation during mitosis and meiosis [48]. These all play important roles in cell development and functions that can affect the regulation of inflammation.

Histone modifications are often positively or negatively correlated with each other, suggesting that variation in the modifications of one histone can be associated with changes in other histone modifications. Evidence has shown that there is a cross-talk among H3S10-p, H3K9ac, and H3K9me2 [49]. Our results show that FOXP3 overexpression increased the levels of H3S10-p, H3K9ac and H3K9me2, potentially indicating crosstalk between histone acetylation and methylation. For example, H3K79me2 is positively associated with histone hyperacetylation, whereas H3K9me2 is positively associated with hypoacetylation. The increases in these modifications that are caused by FOXP3 may not actually occur via the same histone molecules. Because it is a transcription factor, FOXP3 can both activate and inhibit gene expression. Correlated changes in H3 modifications therefore reflect the multiple regulatory mechanisms of FOXP3.

In our work, hypoxia increased H3 post-translational modifications, and FOXP3 negatively affected these increases. FOXP3 delayed the up-regulation of histone methylation, acetylation, and phosphorylation under hypoxic conditions. It is clear that hypoxia can induce inflammation, and that FOXP3 often suppresses it. These opposing effects may be related to the different functions of FOXP3 and hypoxia during inflammation.

Here, we showed that UV induced a global decrease in H3 modifications and, G1/S arrest in and increased apoptosis. FOXP3 delayed the up-regulation of histone demethylase and/or delayed the down regulation of acetyltransferase in cells exposed to UV radiation. When analyzing changes in the cell cycle in otherwise untreated cells, over-expression of FOXP3 increased the proportion of cells in S phase and decreased the proportion in G2/M phase cells, exposure to UV radiation caused no significant changes by FOXP3. UV also had a weaker impact on cell apoptosis, and the effect of UV on cell apoptosis was merged with the effect of FOXP3.

As an intrinsic negative regulator of T cells, the functions of TRAF6 are very different from those of FOXP3. When TRAF6 was pre-overexpressed, additional overexpression of FOXP3 reduced global levels of H3K9ac, H3K18ac, H3K9me2, and H3K79me2. Although H3K18ac, H3K9me2 and H3K79me2 were down-regulated by UV radiation, they were conversely significantly up-regulated by hypoxia in TRAF6-FOXP3 transfected cells. We then analyzed the cell cycle and found that, no clear difference appeared between the effects of treatment
with TRAF6 alone and TRAF6-FOXP3 co-transfection. We observed an increase in apoptosis in TRAF6-FOXP3 co-transfected cells. Under hypoxic condition, TRAF6-FOXP3 co-transfected cells showed only a small decrease in the proportion of cells in S and G2/M phase, whereas the ratio of cells in apoptosis was increased. Interestingly, FOXP3 decreased H3 modifications in cells that co-overexpressed TRAF6 (Figure 5) or were exposed to hypoxia (Figure 2). However, when FOXP3 was co-overexpressed with TRAF6 under hypoxic conditions, H3 modifications were significantly increased. There may be some internal interaction between TRAF6 and hypoxia that re-modified the pattern of FOXP3 to influence H3 modifications. All of the phenomena may help us increase our knowledge of the networks downstream of FOXP3. Determining how FOXP3 interacts with TRAF6 in H3 modifications requires further study.

Moreover, aberrations in histone modifications are also frequently involved in tumorigenesis, and tumor progression, metastasis and prognosis, because cancer is a disease that results from genetic mutations and epigenetic alterations [50]. Data indicates that FOXP3 is expressed in some types of tumors, including breast cancers, prostate cancers, cutaneous melanoma and epithelial ovarian cancer. It has been proposed as a suppressor or treatment of these tumors [51-54]. The detailed functions of FOXP3 in cancers are not as clear as those of Tregs. Overexpression of FOXP3 was found to alter histone H3, we therefore anticipated that mechanisms link FOXP3 to the epigenetic profiles of cancers. Manipulating the post-translational modifications that are mediated by histone H3 is probably one of the main mechanisms by which FOXP3 fulfills its functions in cancer cells and Tregs. Our work is a key step forward that increases our understanding of the functions of FOXP3 in carcinogenesis and provides a novel view of antitumor mechanisms involving FOXP3.

Multiple factors are involved in inflammatory dermatitis, including factors that affect epidermal differentiation and proliferation, the cell cycle, apoptosis, immunity, and inflammation. Our observations on this topic suggest that the impact of FOXP3 on H3 modification marks could be of fundamental importance to the biological nature and clinical behaviors of these diseases. The results of our study indicate that, FOXP3 represents a very attractive target for drug discovery programs aimed at preventing autoimmune dermatitis and other human diseases including cancers, because a large number of studies have shown that histone H3 is an important players in the control of gene expression, genome stability, and cell proliferation.

Acknowledgements

This work was partially supported by the National Natural Science Foundation of China (No. 81373237 and No. 81371729).

Disclosure of conflict of interest

None.

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