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IMMUNE DEFICIENCY AND DYSREGULATION (DP HUSTON AND C KUO, SECTION EDITORS)

Epigenetic Dysfunction in Turner Syndrome Immune Cells

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Abstract Turner syndrome (TS) is a chromosomal condition associated with partial or complete absence of the X chromosome that involves characteristic findings in multiple organ systems. In addition to well-known clinical characteristics such as short stature and gonadal failure, TS is also associated with T cell immune alterations and chronic otitis media, suggestive of a possible immune deficiency. Recently, ubiquitously transcribed tetratricopeptide repeat on the X chromosome (UTX), a histone H3 lysine 27 (H3K27) demethylase, has been identified as a downregulated gene in TS immune cells. Importantly, UTX is an X-linked gene that escapes X-chromosome inactivation and thus is haploinsufficient in TS. Mice with T cell-specific UTX deficiency have impaired clearance of chronic viral infection due to decreased frequencies of T follicular helper (Tfh) cells, which are critical for B cell antibody generation. In parallel, TS patients have decreased Tfh frequencies in peripheral blood. Together, these findings suggest that haploinsufficiency of the X-linked UTX gene in TS T cells underlies an immune deficit, which may manifest as increased predisposition to chronic otitis media.

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Introduction

Turner syndrome (TS) is a common chromosomal abnormality, occurring in about 1:4000 live births, which describes phenotypic females with either partial or complete absence of one sex chromosome [1]. TS is named for Dr. Henry Turner who in 1938 described seven women with short stature, sexual immaturity, cubitus valgus, webbed neck, and low posterior hairline [2]. In the mid 1950s, advances in cytogenetic identification allowed the discovery that patients with TS have one normal X chromosome and a missing or structurally altered sex chromosome [3]. In 1965, after analyzing hundreds of karyotypes of patients with various forms of gonadal dysgenesis, Dr. Malcolm Ferguson-Smith proposed that short stature and other TS clinical findings were due to gene deletions from the missing short arm of the X chromosome [4]. This hypothesis was largely validated in subsequent years [5].

In non-Turner 46 XX females, one copy of the X chromosomes is inactivated to achieve some degree of balanced gene expression between males and females. Thus, absence of one sex chromosome, on the surface, would not be predicted to have any effect. However, X inactivation is incomplete; 15 % of the genes on the silenced X chromosome escape inactivation and are expressed from both chromosomes [6]. Most genes escaping X inactivation are pseudoautosomal genes located on the short arm of the X chromosome and have homologous genes on the Y chromosome. Therefore, most abnormalities seen in TS are thought to be due to haploinsufficiency of genes that are normally expressed by both X chromosomes (Fig. 1a) [1, 6].

Strong evidence for the concept that pseudoautosomal genes underlie TS findings came from the identification of

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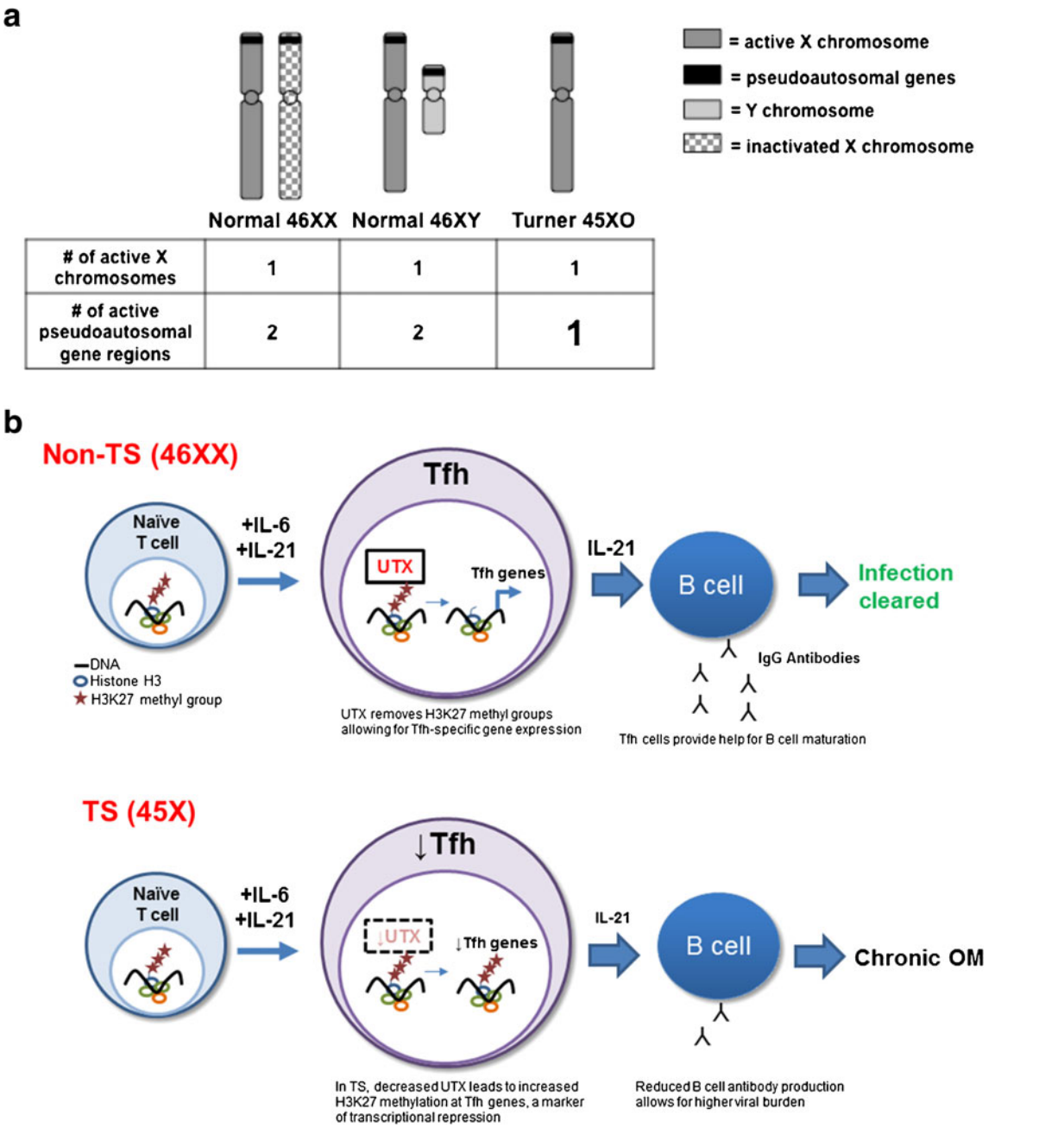

Fig. 1 **a** TS patients are haploinsufficient in pseudoautosomal genes including UTX. Because pseudoautosomal genes escape inactivation, they are expressed from two copies of the X chromosomes in 46XX females. They are also expressed on the Y chromosome, so they are expressed from two copies in 46XY males. In 45XO TS females, however, they are only expressed from one X chromosome, so they may be haploinsufficient in TS. **b** Model: UTX deficiency in TS patients predisposes to chronic viral infection due to impaired Tfh differentiation. In 46XX females haplosufficient for UTX, Tfh cells differentiate from naïve $CD4^+$ T cells through UTX-specific H3K27 demethylase activity. H3K27 demethylation results in increased expression of Tfh-specific genes and adequate Tfh help for B cell maturation, anti-viral antibody production, and virus clearance. However, in TS patients and in UTX-deficient mice, UTX haploinsufficiency results in decreased circulating Tfh cells due to H3K27 methylation and transcriptional suppression of Tfh-specific genes. Decreased Tfh cells in turn reduces B cell antibody production and prolongs chronic infection

short stature homeobox-containing gene (SHOX) as the underlying cause of short stature in TS. SHOX is a pseudoautosomal gene that escapes X inactivation and is highly expressed in osteogenic tissue [7, 8]. Mutations in SHOX cause familial short stature in a dominant fashion, suggesting that a quantitative decrease in the SHOX gene product is sufficient to decrease linear growth [9, 10]. Thus, SHOX haploinsufficiency in TS is a major contributor to growth failure in TS [8, 11]. Together, this evidence suggests that the absence of the genetic material from the missing sex

chromosome results in TS clinical findings. However, other pseudoautosomal X-linked genes that contribute to the TS phenotype remain to be identified.

A deeper understanding of the genetic underpinning of TS and associated clinical features are needed for the development of better prevention, treatment, and anticipatory guidance strategies for TS patients and their families. An area in need of study is the potential alterations in the TS immune system. This review will discuss the current literature regarding TS and associated immune abnormalities and will highlight the role of a pseudoautosomal gene UTX recently discovered to affect $CD4^+$ T cell differentiation and immune defenses against chronic viral infection.

Turner Syndrome May Be Associated with Immune Abnormalities

TS patients are predisposed to a wide array of clinical findings, including frequent otitis media (OM) (Table 1). The pathogenic mechanism underlying this susceptibility to OM is unclear. One hypothesis is that craniofacial features of TS predispose to chronic OM [12]. Another hypothesis that is not mutually exclusive is that an underlying immune deficiency may be a component of TS and contribute to chronic OM. Consistent with this latter possibility, TS patients have been reported to have immune alterations in T cell and immunoglobulin subsets. These include decreased levels of circulation T and B lymphocytes, reduced levels of serum IgG and IgM, and increased IgA [13–15]. However, other studies did not find major immunological deficiencies in TS subjects [16, 17, 18•]. Thus, more research focused on immune alterations in TS subjects is needed to resolve these discrepancies. A confounder for these analyses is that frequent infections, such as in TS, may cause elevated immune activation compared to non-TS controls. Thus, a careful experimental design which take such confounders into consideration is essential.

Table 1 Characteristics and comorbidities in Turner syndrome

Characteristic	Prevalence (%)
Growth abnormalities	90
– Short stature	
Reproductive abnormalities	90
– Ovarian failure	
Dermatologic abnormalities	90
– Multiple pigmented nevi	
– Edema of the extremities	
– *Vitiligo*	
– *Alopecia*	
Neck abnormalities	70
– Webbed neck	
– Low posterior hairline	
Chest abnormalities	70
– Shield chest	
– Wide spaced nipples	
Otologic abnormalities	50
– *Otitis media*	
– Hearing loss	
– Low set ears	
Renal abnormalities	50
– Horseshoe kidney	
– Renal agenesis	
Cardiovascular abnormalities	50
– Coartaction of the aorta	
– Hypertension	
– Bicuspid aortic valve	
Skeletal abnormalities	50
– Short 4th metacarpals	
– Madelung deformities	
– Cubitus valgus	
Endocrine abnormalities	50
– *Autoimmune hypothyroidism*	
– *Carbohydrate intolerance*	
Gastrointestinal abnormalities	30
– Fatty liver disease	
– *Celiac disease*	

Clinical characteristics of TS patients and their prevalence. Potential immune-mediated findings are highlighted in italics. Characteristics secondary to lymphatic obstruction are in underline. Reference: [44]

TS Patient Immune Cells Express Decreased UTX, a Histone-Modifying Enzyme

To determine whether gene expression in immune cells were altered in TS and also to identify potential pseudoautosomal X-linked genes that contribute to immune alterations, Cook et al. performed a microarray analysis on peripheral blood mononuclear cells (PBMCs) comparing gene expression in control females to TS subjects with confirmed 45X karyotype [19••]. A total of 1169 unique genes showed differential expression in TS PBMCs, including 35 on the X chromosome. In particular, ubiquitously transcribed tetratricopeptide repeat on chromosome X (UTX, encoded by *Utx* or *Kdm6a* located at Xp11.3 [20]) was among the top 10 X-linked genes with the largest decrease in expression and the only gene among these candidates that escapes X inactivation [21].

UTX is part of the Jumonji D3 (Jmjd3) family of histone H3 lysine 27 (H3K27) demethylases that epigenetically regulates gene expression (Fig. 1b) [22]. Epigenetic regulation refers to heritable changes in gene expression that do not involve changes in the DNA sequence. Lineage specification is maintained by epigenetic changes that are retained in cells and daughter cells after cell division. For example, chromatin modifications alter the accessibility of genes to transcription factors and RNA polymerases, thus directly impacting gene expression [23]. Chromatin, the condensed packaging of DNA within eukaryotic cells, consists of nucleosomes that contain 146 base pairs of DNA tightly wound around histones. These histones contain amino acid residues exposed around the nucleosome core, or "tails," that can be biochemically

modified at sites of gene promoters and enhancers. These histone modifications are associated with gene expression or gene silencing. Histone H3 lysine 27 trimethylation (H3K27me3) is a transcriptionally repressive modification typically found in heterochromatin or transcriptionally silenced loci. UTX, as a H3K27 demethylase, removes trimethylated and dimethylated groups at H3K27 residues, thus increasing gene expression. UTX is ubiquitously expressed and plays a major role in several cell processes, such as embryonic development [24, 25], cell cycle regulation [26], hematopoiesis [27], and cancer pathogenesis [28, 29]. However, the role of UTX in immune cells was largely unknown.

$CD4^+$ T cells have also been described to undergo epigenetic modifications during T cell differentiation into T helper subsets (e.g., Th1, Th2, Th17, Treg, Tfh) to ensure a heritable gene expression program specific to each subset [23]. A genome-wide study of H3K27 methylation in both naïve and differentiated T cell subsets revealed that upregulation of subset-defining transcription factors, effector molecules, and cytokine was associated with decreased repressive H3K27me3 marks at these gene regions [30]. Although these findings suggested a potential role for UTX in epigenetic regulation of T cell differentiation, whether UTX actually mediated any of these changes was unclear.

UTX Deficiency in T Cells Prevents Tfh Differentiation and Eradication of Chronic Viral Infection

To investigate the role of UTX in T cells in the immune system, Cook et al. turned to genetic mouse models of UTX deficiency. Because UTX knockout mice are embryonic lethal [24, 25], Cook et al. engineered mice with T cell-specific deletion of UTX to determine how decreased UTX may affect T cell function [19••]. Mice with T cell-specific UTX deficiency show normal clearance of acute viral infection but impaired clearance of chronic viral infection. Furthermore, mice that are heterozygous for T cell-specific UTX deficiency show partially attenuated viral loads, suggesting a dose-dependent UTX function in clearance of chronic viral infection [19••].

During chronic viral infection, $CD4^+$ T helper cells play an important role in boosting the $CD8^+$ cytotoxic T cells and B cell-mediated adaptive immune response. Differentiation of $CD4^+$ T cell to the T follicular helper (Tfh) subset, in particular, is critical for generating an appropriate B cell antibody response as revealed by several human genetic immunodeficiencies [31]. T follicular helper cells interact with immature B cells within follicles of secondary lymphoid tissues to promote B cell somatic hypermutation, class switching, and IgG antibody formation [32–35]. In T cell UTX-deficient mice, the impaired immunity to chronic viral infection was associated with decreased Tfh subset differentiation and fewer germinal centers [19••]. As a consequence, B cell IgG production was also impaired [19••]. Interestingly, UTX deficiency in T cells was associated with increased H3K27me3 at genes (e.g., IL6R) important in Tfh differentiation. Therefore, UTX supports Tfh cell differentiation through demethylation of Tfh signature genes, a process required for eliminating chronic viral infection.

TS Patients Have Decreased Tfh Cells

Following infection, otitis-prone children display reduced cytokine-secreting memory T cells and a poor IgG response relative to children not prone to OM, suggesting poor Tfh cell help to B cell antibody responses in children with chronic OM [36]. It was unclear whether TS patients also have an increased predisposition to chronic OM due to decreased Tfh cells. Although T cell UTX deficiency in mice results in fewer Tfh cells, it was not known whether UTX deficiency in TS subject immune cells would translate to decreased Tfh cells. In humans, $CD4^+CXCR5^+$ cells in peripheral blood are associated with antibody production, which allows them to serve as a measurable substitute of Tfh [37]. The frequency of $CD4^+CXCR5^+$ T cells were reduced by twofold in TS subjects compared to controls [19••]. This suggests that decreased UTX expression in TS patients might increase their predisposition to viral infections due to Tfh cell deficiency and subsequent low antibody levels. Overall, these data suggest that UTX haploinsufficiency in TS patient immune cells has functional consequences: decreased Tfh cells, a subset important in the clearance of chronic OM.

Other Roles for UTX in T Cells

In addition to its effects on Tfh differentiation, UTX is also important for T cell maturation and immune homeostasis. For example, T cell-specific deficiency in both UTX and Jmjd3 (UTX and Jmjd3 double deficiency) prevents thymic egress of T cells resulting in increased numbers of CD4SP mature thymocytes and decreased peripheral T cells [38••]. This effect was associated with increased H3K27me3 at the S1PR1 promoter and a corresponding decrease in surface expression of S1PR1, which is required for mature thymocytes to exit the thymus [38••]. Furthermore, demethylase-defunct UTY failed to rescue CD4SP thymocyte S1PR1 expression in UTX and Jmjd3-deficient males, supporting the notion that H3K27 demethylase activity directly results in S1PR1 expression [38••]. Accumulation of thymic CD4SP thymocytes was not noted in mice with T cell-specific UTX deficiency by itself [19••], suggesting that Jmjd3 may be able to compensate, at least in part, for UTX deficiency during T cell thymic egress.

In addition to its H3K27 demethylase activity, UTX can also regulate gene expression in a demethylase-independent manner through protein interactions with chromatin remodeling complexes, such as Brg1, and transcriptional protein complexes. For example, UTX interacts with Th1-specific transcription factor T-bet and the Brg1-containing SWI/SNF remodeling complex in primary human T cells to upregulate interferon gamma (*Ifng*) expression [39], independent of its demethylase activity [39]. It is therefore plausible that UTX may play both a demethylase-dependent and independent role in T cell subset differentiation. Indeed, ChIP-seq experiments in UTX-deficient T cells reveal several gene loci for which gene expression is differentially regulated, but no H3K27 methylation changes were detected [19••, 38••]. Further investigation is needed to determine whether gene expression in TS T cells is also regulated by demethylase-independent UTX function.

Conclusions and Future Directions

TS association with chronic OM is well-recognized, but whether immune abnormalities contribute to this association had not been established. Recent gene expression profiling suggests alterations in TS immune cells and, in particular, highlighted reduced T cell expression of UTX, which may lead to decreased Tfh cells in TS. Of note, genetic deficiency of the UTX gene results in the genetic disorder Kabuki syndrome (KS), a rare congenital disorder that is also associated with recurrent OM [19••, 20]. Furthermore, reduced immunoglobulin levels, hypogammaglobulinemia, poor vaccine response, and reduced memory T and B lymphocytes have also been reported in KS [40, 41]. These associations in KS lend support to the role of UTX in regulating T cell development and immune function.

Recent inroads into understanding the TS immune system also provoke a number of questions. First, how does reduced UTX expression affect other immune cells in TS? It is important to note that the role of UTX was studied in a mouse model in which UTX was lacking in T cells. Whether UTX also regulates other immune cell lines, such as B cells, dendritic cells, macrophages, and neutrophils, is still unclear and requires further study. Second, does reduced UTX expression contribute to TS predisposition to autoimmunity? Autoimmune hypothyroidism and celiac disease are strongly associated with TS, and what underlies this predisposition to autoimmunity is controversial. In one study, defective regulatory T cells (Tregs) that fail to inhibit proliferation of effector T cells were described in TS patients [18•]. Another study, however, found no difference in Treg frequencies or function in TS patients [42]. Thus, the mechanism underlying TS predisposition to autoimmunity remains to be defined.

Third, how do other epigenetic alterations regulate immune cells in TS? Recently, altered DNA methylation patterns, another type of epigenetic modification, of multiple autosomal genes involved in bone remodeling, glucose sensitivity, and ovarian function were reported to be altered in TS [43•]. Thus, it is possible that multiple epigenetic mechanisms of gene regulation are dysregulated in TS. Whether changes in DNA methylation impact T cells in TS requires further study.

Finally, the finding of decreased Tfh cells in TS suggests impaired response to viruses and vaccines. How do TS patients respond to commonly administered vaccine? Should TS patients receive a different course of vaccination? These questions are best addressed in the context of vaccine administration so that a specific T cell response can be measured. Additionally, whether decreased immunoglobulins, possibly as a result of decreased Tfh cells, is a clinical feature of TS is currently unclear and deserves further exploration. If a proportion of TS subjects are found to have lower immunoglobulins, treatment with IVIG may be beneficial to these patients. Even though more work needs to be done in the field of immunity and TS, the discovery of UTX as a gene with decreased expression in TS immune cells and the mechanism by which UTX affects Tfh differentiation are important steps toward understanding immune alterations in TS.

Compliance with Ethics Guidelines

Conflict of Interest Drs. Thrasher, Hong, Whitmire, and Su declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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