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NLRC5/CITA: a novel regulator of class I major histocompatibility complex genes

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In 1936, Peter Gorer reported one of the most significant work in the history of immunology; the first identification of alloantigen using serum from immunized rabbits and his own blood (1). This led to the discovery of the Major Histocompatibility Complex (MHC) by his coworker, George Snell at the Jackson Laboratories. After three quarters of a century, this year, 5 laboratories independently reported that mice deficient for NLRC5 display impaired expression of MHC class I molecules, confirming that NLRC5 is a MHC class I transactivator. What does this mean to us?

MHC has been considered as one of the most important gene family in modern medicine. Research on MHC led to the Nobel prize three times; Peter Medawar in 1960, Baruj Benacerraf, Jean Dausset and George Snell in 1980, Peter Doherty and Rolf Zinkernagel in 1997. As a platform of antigen presentation to T cells and as a major alloantigen in transplanted organs, MHC molecules play critical roles in infectious and inflammatory diseases, cancer and transplantation medicine. Both MHC class I and class II genes are induced during infection and inflammation, thus the tight control of MHC gene expression is necessary for appropriate responsiveness to antigen loads from either inside or outside of cells. However, the mechanism of regulation of MHC gene expression has been largely unknown until the 1990's. Bernard Mach at the University of Geneva discovered the first transactivator of MHC genes by studying patient samples of bare lymphocyte syndrome (BLS), a group of hereditary diseases manifesting impaired MHC class II expression (2). His group named it MHC class II transactivator or CIITA. CIITA itself has no DNA-binding domain. However, by interacting with transcription factors at the promoter of MHC class II, CIITA generates an active protein-DNA complex called "MHC enhanceosome" which drives the activation of MHC class II genes (3). A striking feature of CIITA is that it is required not only for the expression of MHC class II (HLA-DP, -DQ and -DR) genes but also for that of the regulatory molecules involved in the MHC class II pathway including the invariant chain, HLA-DO and -DM (4). Therefore, CIITA is critical in orchestrating the expression of genes involved in the MHC class II pathway. Because of its requirement for both constitutive and inducible expression of MHC class II, CIITA has been referred to as a master regulator of MHC class II genes (5). Interestingly, CIITA can activate not only the promoters of MHC class II genes but also of MHC class I genes at least in *in vitro* experiments (6-10). However, mutations in the CIITA gene in human BLS patients and deficiency of CIITA in mice did not show any reduction of MHC class I (2, 11-14). This led to the obvious assumption that a similar unknown transactivator should exist for the regulation of expression of MHC class I genes.

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Seventeen years after the discovery of CIITA, the MHC class I transactivator was identified. Similar to CIITA, it is a member of NLR (nucleotide binding domain-leucine rich repeats containing) family of proteins, called NLRC5 (15, 16). NLRC5 has unusually long leucine-rich repeats and its N-terminal structure was different from that of CIITA (16, 17). Because of this, these two proteins look very different at first sight. However, upon detailed phylogenetic analysis of the nucleotide binding domain, it became clear that NLRC5 is the most closely related to CIITA among all NLR proteins (15, 18). NLRC5 or MHC class I transactivator (CITA) as we now know, does not carry an apparent DNA-binding domain. However, NLRC5/CITA can translocate into the nucleus due to its NLS (nuclear localization signal) and associate specifically with MHC class I promoters (15, 18). The nucleotide binding domain of NLRC5 is required for both nuclear translocation and transactivation of MHC class I genes (19). Similar to MHC class II genes, MHC class I genes share similar *cis*-regulatory elements in their proximal promoters, termed W/S, X1, X2 and Y-box motifs, which are occupied by similar transcription factor complexes (5, 9, 10, 20). It has been demonstrated that NLRC5 can associate with the RFX transcription factor complex at the X1 box through association with one of the RFX factor subunits, RFXANK/B via its ankyrin repeats (21). Also NLRC5 can cooperate with ATF1/CREB family transcription factor at the X2 box of MHC class I promoter (21). Moreover, NLRC5 cooperates with other transcriptional co-activators, which possess histone acetyltransferase activity, such as CBP/p300, GCN5 and PCAF (21), suggesting that NLRC5 is capable of opening the chromatin structure of MHC class I gene locus. NLRC5 is highly inducible by IFN- γ stimulation and modestly by IFN- β stimulation (15, 17, 18, 22). This explains the mechanism of induction of MHC class I during inflammation. IFN- γ stimulation induces MHC class II expression via upregulation of CIITA in hematopoietic cells (23). Similarly, IFN- γ can induce MHC class I expression via upregulation of NLRC5/CITA (16). Furthermore, NLRC5 is not merely a co-activator of MHC class I genes. NLRC5 can also induce class I related genes required in MHC class I antigen presentation, such as β 2-microglobulin, TAP1 and LMP2 (15). Therefore, NLRC5 regulates concerted expression of genes involved in MHC class I pathway (16).

Unlike CIITA mutations in BLS patients, hereditary MHC class I deficiency is extremely rare. Therefore, animal models are necessary to examine the impact of NLRC5/CITA deficiency *in vivo* on MHC class I expression and infectious diseases. Recent reports from 5 groups using NLRC5-deficient mice clarified this question. NLRC5 deficiency resulted in impaired expression of MHC class I at transcriptional, protein and surface expression levels (24-28). The expression of MHC class II, on the other hand, is intact in all cell types, confirming that NLRC5 is required solely for MHC class I gene expression (24, 26-28). IFN- γ stimulation could not rescue the phenotype of impaired MHC class I expression, indicating that NLRC5/CITA is required for both constitutive and inducible expression of MHC class I (24). In addition to classical MHC class I (MHC class Ia), the expression of non-classical class I (MHC class Ib) was also impaired (24, 27, 28). Moreover, the expression of class I related genes, β 2-microglobulin, TAP1 and LMP2, was reduced in NLRC5-deficient mice (24, 27, 28). Although MHC class I expression is impaired in both lymphoid and non-lymphoid organs in NLRC5-deficient mice, the requirement of NLRC5 varies among tissues and cell types (24). The reduced MHC class I expression was most prominent in CD4 and CD8 T cells and less in B cells (24-26, 28). Interestingly, macrophages and dendritic cells retained substantial residual MHC class I expression. Similar phenotype was also observed in CIITA deficient mice where dendritic cells retain residual MHC class II expression (14). These facts suggest that antigen presenting cells may have alternative mechanisms to ensure the efficient presentation of antigens to T cells in both MHC class I and class II pathways. Two groups showed the impact of NLRC5 deficiency on infectious diseases using intracellular bacterium, *Listeria monocytogens*.

Listeria infected NLRC5-deficient mice exhibited impaired activation of CD8 T cells, resulting in higher susceptibility with high bacterial burden in various organs (24, 27).

In addition to previous reports, these studies using NLRC5-deficient mice undoubtedly accelerate the field of MHC research. Until very recently, the regulation of MHC class I expression was poorly understood. The significance of MHC class I in infectious diseases, cancer, organ rejection during transplantation and other diseases has been well known, particularly based on the results of studies using MHC class I deficient mice such as β 2-microglobulin deficient mice and H2-K, H2-D double deficient mice. However, controlling activity of diseases aforementioned by intervening MHC class I expression itself has been barely tried, largely because the regulatory mechanism was not known. Having better picture of MHC class I gene regulation and animal models, it is now possible to manipulate the MHC gene regulation for further clinical interventions in various diseases.

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