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AUTOIMMUNITY

HLA-mediated protection in Goodpasture disease

> HLA allelic polymorphisms result in structurally important differences in presentation of the critical T-cell epitope of the disease-causing autoantigen

A new study provides insights into the molecular mechanisms of HLA-mediated susceptibility and protection in Goodpasture disease (GPD). This rare renal disorder is characterized by autoimmune responses to the non-collagenous domain of the α3 chain of type IV collagen (α3(IV)NC1). Expression of HLA-DR15 is associated with an increased risk of GPD, but this risk is reduced to baseline in the presence of the protective HLA allele HLA-DR1.

"The basis of the loss of immunological tolerance in most autoimmune diseases lies in the inheritance of HLA alleles that modulate the risk of autoimmunity," explains researcher Richard Kitching. "In this study we used GPD to address two long-standing questions — what is the basis of HLA-mediated protection in autoimmune disease and how does a protective allele mitigate the excess risk conferred by a susceptibility allele?"

The researchers focused their investigations on the immunodominant T-cell epitope of α3(IV)NC1, $\alpha3_{135–145}$. Using HLA-DR15-$\alpha3_{135–145}$ tetramers, they showed that $\alpha3_{135–145}$-specific $CD4^+$ T cells were 100-fold more frequent in the peripheral blood of $HLA\text{-}DR15^+$ patients with GPD than in $HLA\text{-}DR15^+$ healthy controls. In seven of the eight patients, these epitope-specific cells were mainly conventional $FOXP3^-$ T cells. Consistent with a protective role of HLA-DR1 in GPD, immunization with $\alpha3_{135–145}$ led to renal infiltration of $\alpha3_{135–145}$-specific $CD4^+$ T cells and the development of GPD in $HLA\text{-}DR15^+$ transgenic mice, but did not induce proinflammatory autoreactivity to $\alpha3_{135–145}$ in $HLA\text{-}DR15^+DR1^+$ transgenic mice.

To determine the molecular basis of the protective effect of HLA-DR1, the researchers characterized the self-peptide repertoires of HLA-DR1 and HLA-DR15 allomorphs from naive $HLA\text{-}DR1^+$ and $HLA\text{-}DR15^+$ mice and identified consensus peptide-binding motifs. They report that these HLA alleles have distinct self-peptide repertoires and $\alpha3_{135–145}$-binding registers. These differences result in the presentation of distinct peptide-HLA landscapes to T cells, which in turn lead to differences in the responding T-cell repertoires.

Further investigations indicated that $\alpha3_{135–145}$-specific $CD4^+$ T cells from transgenic mice that express HLA-DR15, HLA-DR1 or both HLA alleles have functional phenotypic differences. In $HLA\text{-}DR15^+$ mice, the majority of these cells were conventional $Foxp3^-$ T cells that secreted proinflammatory cytokines, whereas in $HLA\text{-}DR1^+$ mice the majority of the epitope-specific $CD4^+$ T cells were $Foxp3^+$ regulatory T (T_{reg}) cells that secreted tolerogenic cytokines. $HLA\text{-}DR15^+DR1^+$ mice expressed both conventional and regulatory $\alpha3_{135–145}$-specific $CD4^+$ T cells. Analysis of the phenotypes of $\alpha3_{135–145}$-specific $CD4^+$ T cells from healthy people who were either homozygous for HLA-DR1 or HLA-DR15, or were heterozygous for these HLA alleles, gave similar results.

Finally, the researchers showed that $\alpha3_{135–145}$-specific $CD4^+$ T_{reg} cells generated in the context of HLA-DR1 suppress autoreactive conventional $\alpha3_{135–145}$-T cells generated in the context of HLA-DR15, so maintain self-tolerance to $\alpha3_{135–145}$ and protect against the development of GPD.

"HLA allelic polymorphisms result in structurally important differences in presentation of the critical T-cell epitope of the disease-causing autoantigen," concludes Kitching. "These differences result either in the generation of conventional autoantigen-specific $CD4^+$ T cells (in the context of the risk allele, HLA-DR15) or of dominantly protective antigen-specific T_{reg} cells (when the epitope is presented by the protective HLA allele, HLA-DR1). These findings provide a structural and mechanistic basis for understanding HLA-mediated susceptibility and protection in autoimmune disease."

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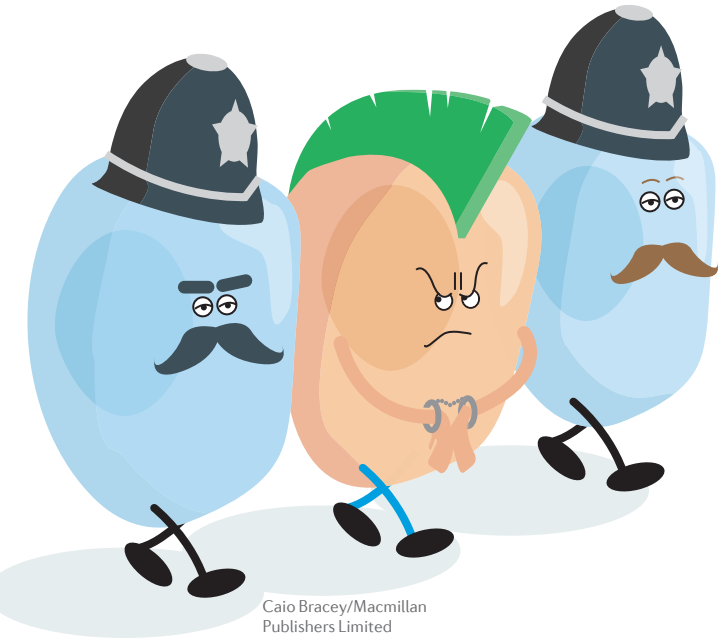

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