MICROBIOLOGY AUSTRALIA, 2021, 42, 84–86
https://doi.org/10.1071/MA21020

HLA and immunodominance in viral infection: T-cell responses in protection and immunopathogenesis

Allison Imrie[A,B] *and Suzi McCarthy*[A]

[A]School of Biomedical Sciences, University of Western Australia and PathWest Laboratory Medicine WA, WA, Australia
[B]Email: allison.imrie@uwa.edu.au

Abstract. The protective role of T cells in viral infection is well described. T cells generally mediate anti-viral immune responses via direct cytotoxicity and production of pro-inflammatory cytokines, by providing help to B cells and by promotion of memory responses. A fundamental step in T cell responses involves presentation of viral peptide antigens in the context of human leucocyte antigens (HLA), to the T-cell receptor. HLA are highly polymorphic cell surface molecules that present a vast array of peptides to T cells and induce their activation, differentiation and proliferation into effector cells which can eliminate microbial infection.

Received 5 May 2021, accepted 11 May 2021, published online 20 May 2021

The human HLA molecules were first identified in the early 20th century as transplantation antigens and characterised in the 1950s as transfusion antigens. In 1974 Rolf Zinkernagel and Peter Doherty[1] described the phenomenon of MHC restriction – that killing of virus-infected cells by mouse cytotoxic T cells depended on a combination of viral antigen and mouse H-2 (murine HLA) antigen. Subsequent work over the next decades showed that the human MHC (Major Histocompatibility Complex) encodes the classical MHC Class I and Class II HLA molecules, which present peptide antigens to $CD8^+$ and $CD4^+$ T cells, respectively. The Class I MHC encode the HLA-A, HLA-B, and HLA-C molecules involved in peptide antigen presentation to $CD8^+$ T cells, and the Class II genes encode the HLA-DP, HLA-DQ, HLA-DR molecules that present peptide antigens to $CD4^+$ T cells. Each of the MHC genes is highly polymorphic, encoding a large number of variants differing by up to 20 amino acids and which are capable of binding different peptides; differences within these variants are largely within the peptide-binding sites that make direct contact with the T-cell receptor. More than 20 000 different Class I and Class II alleles have been identified so far[2].

HLA Class I molecules are expressed on the surface of almost all nucleated cells. Class II molecules are constitutively expressed on immune cells including professional antigen presenting cells (dendritic cells, macrophages and monocytes), B cells and activated T cells, and expression can be induced on most cells by interferon-gamma. T cells recognise peptide antigens bound to HLA molecules, as peptide/MHC (pMHC) complexes, via their T-cell receptors. Activated naïve T cells undergo clonal expansion to effector cells that mediate protective immune responses including cytokine secretion and cytotoxicity, and a small percentage of effector cells become long lived memory cells which can be reactivated to mediate protective immunity when the host is challenged months or years later. As all nucleated cells can express class I MHC, activated CTL can kill any infected cell in any tissue and significantly reduce the reservoirs of infection. CTL are critical for control of many acute viral infections and provide protection against secondary infections.

After entering a cell, viruses initiate translation of their proteins. Proteins within the cytosol enter the proteosome where they are cleaved to peptides 8–12 amino acids long. These peptides are transported into the endoplasmic reticulum where they associate with newly synthesised MHC Class I molecules, and the pMHC complex is transferred to the surface of the infected cell where it can interact with the T-cell receptor of $CD8^+$ T cells. Of the thousands of peptides encoded by a virus that can be presented to T cells, in association with a given MHC Class I allele, only a small number of immunodominant peptide antigens induce a response. Class I polymorphism is thought to have evolved as a protective function of the immune response to the large array of microbes we encounter, including emergent and re-emergent viruses, and to protect against pathogen immune evasion. However, both protective and dysfunctional HLA-associated T-cell responses have been described.

Escape from CTL-mediated immune control was first described for HIV-1 in 1991[3]. HLA-B*27-positive HIV-infected individuals are among the elite controllers, antiretroviral-naïve subjects with undetectable viral loads. The HLA-B*27-restricted response to the immunodominant HIV GAG 263-272 KK10 epitope was shown to be associated with slow progression to disease. Mutation within this epitope that prevented peptide attachment to the binding cleft of the Class I molecule abrogated immunogenicity for any HLA-B*27-

positive recipient of the variant virus. Escape mutants were associated with progression to AIDS[4]. Following recognition of the role of HLA in control of HIV replicative capacity, other Class I molecules were linked to protective responses. HLA-mediated control of HIV has been well described within the sub-Saharan African population, in the context of HLA-B*57 and HLA-B*58-restricted HIV p24 Gag-specific responses. The immunodominant HLA-B*57:03-restricted GAG 162-172 KF11 epitope is targeted by the majority of infected individuals expressing HLA-B*57:03. Escape within KF11 is similar to that described for HLA-B*27-KK10 where mutation is at the residue that anchors the peptide to the HLA binding cleft, and can lead to loss of recognition of the epitope by $CD8^+$ T cells if compensatory mutations do not restore viral fitness. These CTL responses directed against the more conserved HIV Gag protein are more effective in long term suppression of viremia than responses against less conserved viral proteins, including HIV Env, which do not have a significant impact on HIV replication capacity and are not associated with control of viremia[5,6]. Genome-wide association studies identified the HLA-peptide binding region as the major factor modulating control of HIV-1 replication in elite controllers[7], supporting the findings of *in vitro* analyses of T-cell function; however, subsequent assessment of HLA-B*57- and HLA-B*27-restricted CD8 T cells showed that elite controllers were differentiated from progressors who expressed the same alleles, on the basis of potency and cross-reactivity of T-cell receptor recognition of HIV-1. The protective effect of HLA alleles is therefore modulated by host TCR usage, which determines viral replication capacity and evolution of immune escape variants[8].

In dengue virus (DENV) infection virus-specific T-cell responses have been shown to be both protective and pathologic. Primary DENV infection induces long lasting immunity[9] to the same DENV serotype but does not provide long term protection against infection with the other three serotypes and people who live in dengue endemic areas will likely be infected multiple times over their lifetimes. Pre-existing cross-reactive memory T cells may be preferentially reactivated to mount an ineffective anti-viral response which does not control viral replication; higher viremia is associated with increased likelihood of developing severe dengue[10]. This phenomenon of original antigenic sin in dengue-specific T-cell responses was described in a Thai population, with HLA-A*11 found in 30% of the southeast Asian population, presenting DENV NS3 130-144 GTS epitope[11]. $CD8^+$ memory T cells in acute phase DENV infection preferentially bound tetramers constructed with serotype-specific GTS epitope peptide variants representing possible earlier dengue infections, and there was an association between magnitude of the T-cell response and disease severity. Skewed memory T-cell responses have been described in other populations: $CD8^+$ T-cell clones specific for an immunodominant HLA-B*55-restricted NS5 329-337 KP9 epitope demonstrated greater functional avidity for variant DENV-2 epitope peptides, in Pacific Islanders recently infected with DENV-1 and who had encountered DENV-2 in a previous epidemic[12].

Polymorphism, particularly in the HLA-A gene, was shown to be associated with increased susceptibility to dengue haemorrhagic fever/severe dengue in a Vietnamese population[13], where HLA-A*11 and HLA-A*24 were considered susceptible genotypes that present epitopes, in the relatively conserved DENV NS3 and NS5, that are both serotype-specific and cross-reactive. Such potentially serotype cross-reactive $CD8^+$ T cells are postulated to contribute to dengue immunopathogenesis in endemic settings that experience regular epidemic transmission of variant DENV. Another study in more than 600 Vietnamese children with severe dengue found the same association with HLA-A*24, where the A*2402/03/10 allele with altered structure in the peptide binding pocket was expressed at higher frequency in children with severe dengue compared to population background groups[14].

Other population-based studies have shown strong protective effects of DENV-specific $CD8^+$ T cells, with repeated DENV exposure in Sri Lankan blood donors driving responses towards CTL recognition of relatively conserved non-structural proteins NS3, NS4B and NS5[15]. HLA-B-restricted responses (B*0702, B*3501, B*4001) were of significantly higher magnitude and greater breadth, and were associated with multifunctional T-cell responses with hierarchy IFN-gamma>TNF-alpha>IL-2, compared with HLA-A responses that were of lower breadth and magnitude. These findings were extended in a Nicaraguan population, where despite differences in DENV variants and epidemiology there was also a strong correlation between HLA type and breadth and magnitude of T-cell responses, including immunodominant responses restricted by HLA-B*3501, an allele that was also associated with protection in the Sri Lankan population. As was described in Vietnam, HLA-A*2402 was subdominant and associated with increased susceptibility to severe disease. Interestingly, B*3501-restricted T cells but not HLA-A*2402-restricted T cells expressed PD-1, and in contrast to other viral infections these PD-1+ $CD8^+$ T cells were associated with activation, not exhaustion, and were proliferative and functional. PD-1 may be a marker of activated and highly functional $CD8^+$ memory T cells in DENV infection[16].

An exhausted $CD8^+$ T-cell phenotype has been described in patients with severe COVID-19[17] but not in patients with more mild disease, suggesting that cellular immune responses are protective. $CD8^+$ and $CD4^+$ T-cell epitopes are being mapped and their immunodominance assessed for common and less frequent HLA alleles, across different population groups. Of great interest is the

observed cross-reactivity in SARS-CoV-2 T-cell responses in healthy unexposed people sampled prior to the pandemic[18], raising the issue of whether pre-existing SARS-CoV-2-reactive memory T cells, likely induced in previous human seasonal coronavirus infection, mediate protection or contribute to immunopathogenesis of COVID-19. These data, in association with a greater understanding of SARS-CoV-2-specific T-cell phenotype and function, will advance our understanding of the correlates of protection and immunopathogenesis and importantly, enhance our understanding of how to best optimise COVID-19 vaccine design.

Conflicts of interest

The authors declare no conflicts of interest.

Declaration of funding

This research did not receive any specific funding.

References

1. Zinkernagel, R.M. and Doherty, P.C. (1974) Restriction of in vitro T cell-mediated cytoxicity in lymphocytic choriomeningitis within a sungeneic or semiallogeneic system. *Nature* **248**, 701–702. doi:10.1038/248701a0
2. Robinson, J. *et al*. (2020) PD-IMGT/HLA Database. *Nucleic Acids Res.* **48**, D948–D955. doi:10.1093/nar/gkz950
3. Phillips, R.E. *et al*. (1991) Human immunodeficiency virus genetic variation that can escape cytotoxic T cell recognition. *Nature* **354**, 453–459. doi:10.1038/354453a0
4. Goulder, P.J. *et al*. (1997) Late escape from an immunodominant cytotoxic T-lymphocyte response associated with progression to AIDS. *Nat. Med.* **3**, 212–217. doi:10.1038/nm0297-212
5. Troyer, R.M. *et al*. (2009) Variable fitness impact of HIV-1 escape mutations to cytotoxic T lymphocyte (CTL) response. *PLoS Pathog.* **5**, e1000365. doi:10.1371/journal.ppat.1000365
6. Kiepiela, P. *et al*. (2007) CD8+ T-cell responses to different HIV proteins have discordant associations with viral load. *Nat. Med.* **13**, 46–53. doi:10.1038/nm1520
7. Pereyra, F. *et al*. (2010) The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. *Science* **330**, 1551–1557. doi:10.1126/science.1195271
8. Chen, H. (2012) TCR clonotypes modulate the protective effects of HLA. *Nat. Immunol.* **13**, 691–700. doi:10.1038/ni.2342
9. Imrie, A. *et al*. (2007) Antibody to dengue 1 detected more than 60 years after infection. *Viral Immunol.* **20**, 672–675. doi:10.1089/vim.2007.0050
10. Vaughn, D.W. *et al*. (2000) Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. *J. Infect. Dis.* **181**, 2–9. doi:10.1086/315215
11. Mongkolsapaya, J. *et al*. (2003) Original antigenic sin and apoptosis in the pathogenesis of dengue hemorrhagic fever. *Nat. Med.* **9**, 921–927. doi:10.1038/nm887
12. Imrie, A. *et al*. (2007) Differential functional avidity of dengue virus-specific T cell clones for variant peptides representing heterologous and previously encountered serotypes. *J. Virol.* **81**, 10081–10091. doi:10.1128/JVI.00330-07
13. Loke, H. *et al*. (2001) Strong HLA class I-restricted T cell responses in dengue hemorrhagic fever: a double-edged sword? *J. Infect. Dis.* **184**, 1369–1373. doi:10.1086/324320
14. Lan, N.T.P. *et al*. (2008) Protective and enhancing HLA alleles, HLA-DRB1*0901 and HLA-A*24, for severe forms of dengue virus infection, dengue hemorrhagic fever and dengue shock syndrome. *PLoS Negl. Trop. Dis.* **2**, e304. doi:10.1371/journal.pntd.0000304
15. Weiskopf, D. *et al*. (2013) Comprehensive analysis of dengue virus-specific responses supports an HLA-linked protective role for $CD8^+$ T cells *Proc. Natl. Acad. Sci. USA* **110**, E2046–E2053. doi:10.1073/pnas.1305227110
16. de Alwis, R. *et al*. (2016) Immunodominant dengue virus-specific $CD8^+$ T cell responses are associated with a memory PD-1^+phenotype. *J. Virol.* **90**, 4771–4779. doi:10.1128/JVI.02892-15
17. Zheng, H.Y. *et al*. (2020) Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cell. Mol. Immunol.* **17**, 541–543. doi:10.1038/s41423-020-0401-3
18. Grifoni, A. *et al*. (2020) Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell* **181**, 1489–1501. e15. doi:10.1016/j.cell.2020.05.015

Biographies

Dr Allison Imrie is an Associate Professor in the School of Biomedical Sciences, UWA. Her early work with human immunodeficiency virus (HIV) focussed on virus transmission between transmitter and recipient pairs, including transmission of antiviral drug resistant HIV species. She also characterised immune responses in early HIV infection. She was invited to work with the Global Program on AIDS in the World Health Organization Western Pacific Regional Office as a short-term consultant to advise member states to develop short-and medium-term plans for AIDS prevention and control and to assist with establishing HIV testing and surveillance programs. She then worked on mosquito-borne viral diseases of public health importance including dengue, and investigations of viral molecular epidemiology and immunopathogenesis. She has worked with colleagues in the Asia Pacific region to investigate neglected tropical diseases including dengue, Zika, Chikungunya and leptospirosis, and in Australia with her colleagues and students on endemic viruses including Ross River virus. She collaborates with her colleagues and students in Australia, China and the US to identify novel mosquito-borne viruses. Most recently she has been funded to investigate immune responses in people diagnosed with coronavirus infection.

Suzi McCarthy is Acting Medical Scientist in Charge of Microbiology at PathWest Laboratory Medicine in Perth, Western Australia where she oversees serological testing for Arboviruses and respiratory viruses (including COVID-19). Her research interests include developing and validating new diagnostic assays, and cell mediated immune responses to viral infections. In collaboration with the University of Western Australia, she has been investigating long term persistence of dengue virus-specific T-cell memory in Western Australian returning travellers with well defined monotypic dengue virus infection.