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Harnessing Innate and Adaptive Immunity for Viral Vaccine Design

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The recent Keystone Symposia meeting on HIV Vaccines was held on 21–26 March 2012 in Keystone, Colorado, back-to-back with the Viral Immunity meeting, creating synergy between the two areas of research. In this short review of the meeting, we will highlight three areas of interest that emerged from the two meetings, including the recently emerging role of natural killer (NK) cells in modulating dendritic cell (DC) function, new data on the importance of DC antigen processing on priming of adaptive immunity, and intriguing data suggesting that narrow targeting of very few protective epitopes restricted by a single major histocompatibility complex (MHC) class I allele might be sufficient to mediate control of otherwise highly pathogenic simian immunodeficiency virus (SIV) infection.

Impaired priming of viral-specific T cells in the context of effective NK cell responses

The innate immune system plays a critical role in the establishment of a strong and effective adaptive immune response to vaccines [1]. In the light of recent data suggesting a unique ability of NK cells to shape adaptive T cell responses via their interaction with other immune cells, such as DCs and CD4+ T cells, understanding the impact of interplays between NK cells and other immune cells has become an area of intense interest[2–4].Recent work of Dr. Mariapia A. Degli-Esposti from the University of Western Australia (Perth, Australia) (talk X6-004) has provided new insights into how NK-DC cross-talks affect T cell responses to Mouse Cytomegalovirus (MCMV). The investigators studied virus-specific CD4+ and CD8+ T cell responses indistinct strains of mice that differ in their expression of Ly49H, an activating NK cell receptor that can interact with the MCMV protein m157, thereby activating NK cells and promoting better control of MCMV infection [2,5,6]. A panel of elegant experiments revealed that the frequency and the length of viral antigen presentation by DCs are controlled by NK cells. Potent NK cell responses resulted in enhanced elimination of MCMV-infected DCs, and thereby to a limited ability to sustain ongoing virus-specific T cell proliferation. Similar results were obtained using NK-cell depleted mice infected with lymphocytic choriomeningitis virus (LCMV)in a study presented by Dr. Kevin D. Cook from the Carolina Vaccine Institute at the University of North Carolina (Chapel Hill, NC, USA) (poster X6-121). The absence of NK cells did not

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affect the previously described CD8+ T cell mediated clearance of the LCMV-Armstrong strain. However, NK-cell depleted mice displayed increased rates of viral clearance and enhanced T cell responses when infected with the LCMV clone-13, a strain that usually causes chronic LCMV infection. Altogether, these data demonstrate that the intensity of NK cell response during primary viral infections might be crucial in determining the longevity and the effectiveness of antiviral T cell responses. Further investigations are warranted to eventually harness NK cell function to modulate the quality of the adaptive immune response using immunotherapeutic interventions during vaccinations.

Endogenous versus exogenous mechanisms of adaptive priming

The importance of dendritic cells in recognizing viral infections and initiating the subsequent adaptive immune response is well established. The myriad of mechanisms through which this occurs, however, is still been deciphered. Antigen presentation has classically been shown to involve capture of antigens, processing in late endosomal compartments and subsequent presentation on the cell surface. Dr. Laurence Eisenlohr from Thomas Jefferson University (Philadelphia, PA, USA) highlighted alternative pathways in his plenary talk (X6-010), including the recycling of loaded MHC, the role of proteasome and TAP transporter, and autophagy. Particularly live influenza virus infection induced a much better antigen presentation by MHC class II molecules than inactivated influenza virus, suggesting that viral antigens produced endogenously are much more efficiently presented than those acquired exogenously. For influenza virus infection at least this process was largely influenced by the TAP pathway and not autophagy [7]. However, autophagy has been shown to be important in MHC class II presentation of other viruses. In HIV-1 infection the role of autophagy in antigen presentation still remains to be elucidated. Dr. Arnaud Moris from Marie and Pierre Curie University (Paris, France) (Poster X6-248) showed intriguing new data suggesting that HIV-1 hijacks the autophagy system as a mechanisms for DC-CD4+ T cell transmission [8]. HIV-1 envelope activates mTOR, a negative regulator of autophagy, thereby decreasing autophagosome formation and increasing the presence of HIV-1 particles in DCs. In addition to increasing potential cell-to-cell transmission of HIV-1, this process may potentially also modulate how antigens are process and presented. Dr. Christopher Norbury from Pennsylvania State University (Hershey, PA, USA) presented complementary data to Dr. Eisenlohr in the context of MHC class I, demonstrating difference in antigen presentation between antigens expressed within cells and those acquired exogenously (X6-252 and [9]). Infection of mice with live ectromeliavirus led to an increase in MHC class I expression as compared to when antigens were acquired exogenously, suggesting that the use of live attenuated virus may result in much more efficient CD8+ T cell priming. The role of how antigens are endogenously or exogenously processed will have important implications in the design of future vaccines eliciting adaptive T cell immunity. This may also have implications in how T cell responses are measured, particularly when exogenous peptides are used, as antigen processing and presentation pathways are not accounted for by these approaches.

Protective immunity mediated by very few epitope-specific CD8+ T cells

Infection of rhesus macaques with the highly pathogenic clone SIV_{mac239} leads to high levels of viral replication and rapid progression to AIDS in most infected animals. However, in a subset of SIV-infected rhesus macaques encoding for the protective MHC class I allele Mamu-B*08, viral replication is controlled to low levels in about 50% of infected animals. Dr. David Watkins from the University of Miami (Coral Gables, FL, USA) presented intriguing new data at the HIV Vaccines meeting demonstrating that this control of viral replication is mediated by very few Mamu-B*08-restricted CD8+ T cells directed against 3 immunodominant epitopes in the HIV-1 accessory proteins Vif and Nef (X5-016).

Following vaccination of Mamu-B*08+ rhesus macaques with a vaccine expressing only parts of the SIV proteome encoding for these three immunodominant CTL epitopes, 7/8 SIV infected macaques exhibited elite control of viral replication, compared to the expected 50% of macaques that were immunized with a vaccine only expressing two small regions of the SIV proteome that do not encode for any known Mamu-B*08 epitopes. These results are remarkable, as they suggest that very few potent virus-specific CD8+ T cell responses are sufficient to mediate control of viral replication. A better understanding of the antiviral effector mechanisms that render these CD8+ T cells protective will be critical to extend these findings to other MHC class I alleles that are normally not protective in natural infection. A complementary study (Poster X5-111) by Dr. Todd Allen's lab at the Ragon Institute of MGH, MIT and Harvard (Charlestown, MA, USA) utilized deep sequencing of HIV-1 to examine the impact of early viral evolution on viral control. The authors described that rapid escape from immunodominant CD8+ T cell responses in three acute infected subjects was associated with failure to sustain the initial decline in peak viremia. These data suggest that the rate at which frontline CD8+ T cell responses are lost is an important factor in determining the relative success of the acute immune response against HIV-1. Taken together, these studies support that overcoming the natural immunodominance patterns of T cell responses restricted by common, non-protective human leukocyte antigen (HLA) class I alleles through vaccination to redirect CD8+ T cells towards vulnerable areas of the virus might enable individuals expressing non-protective HLA class I alleles to mount protective immune responses.

Overall, the HIV Vaccines Keystone Symposia included many additional exciting presentations that could not be reported here due to space limitation, including follow-up studies on the RV144 HIV vaccine trial. The development of novel concepts to improve HIV-1 vaccines is currently a major challenge, and having the HIV vaccines meeting together with the meeting on Viral Immunity and Host Gene Influence enabled exciting interactions between these related fields.

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