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Better understanding CD8$^+$ T cells in cancer and viral infections

The first conference on 'Infection and Immunity' was organized by the Institute for Basic Science and Korean Association of Immunologists and held in Daejeon, South Korea, from 12 to 14 July 2023. The conference focused on the biology of CD8$^+$ T cells in the context of viral disease and cancer.

In July 2021, during the COVID-19 pandemic, the Korea Virus Research Institute (KVRI) was established within the Institute for Basic Science (IBS) located in Daejeon, South Korea, with the aim of improving responses to newly emerging viral diseases. In July 2023, the Center for Viral Immunology in the KVRI collaborated with the Korean Association of Immunologists (KAI) to hold the first IBS-KAI conference on 'Infection and Immunity', in which 26 invited speakers presented their research updates (http://virus-immunity.org/). The primary aim of this IBS-KAI conference was to gather researchers specializing in diverse areas of immunology and infection, stimulate meaningful interactions, and establish a platform for reaching mutual agreements based on shared ideas and strategies (Fig. 1). Since CD8$^+$ T cells are direct effectors in adaptive immunity against virus-infected cells or tumor cells, this meeting focused on fostering a cohesive understanding of the characteristics and roles of CD8$^+$ T cells in various disease contexts.

Fig. 1 | Highlights of the first IBS-KAI conference on Infection and Immunity. a, The IBS and the KAI successfully organized the first conference on Infection and Immunity. **b**, The conference featured eminent plenary lectures delivered by Rafi Ahmed and Mark Davis. **c**,**d**, The invited speakers visited the IBS headquarters (**c**) and engaged in an active discussion with the young scientists (**d**).

Dissection of CD8$^+$ T cell exhaustion

In his plenary lecture, Rafi Ahmed (Emory University, USA) described how CD8$^+$ T cells adapt to chronic antigen stimulation — for example, by differentiating from PD-1$^+$TCF-1$^+$ stem-like CD8$^+$ T cells to transitory effector cells and terminally differentiated exhausted cells. In his research, human papilloma virus (HPV)-specific CD8$^+$ T cells were investigated as a surrogate of tumor-specific T cells in patients with HPV-positive head and neck squamous cell carcinoma (HNSCC), leading to the identification of three transcriptionally distinct states of T cell exhaustion[1]. He suggested treating HPV-positive HNSCC by combining PD-1 blockade and therapeutic vaccination targeting the HPV proteins E2, E5, E6 and E7. He also proposed combining PD-1 blockade with IL-2 treatment to change the differentiation trajectory of PD-1$^+$TCF-1$^+$ stem-like CD8$^+$ T cells to exhibit more effector functions with less exhaustion, and to increase the frequency of stem-like CD8$^+$ T cells[2]. Evan Newell (Fred Hutchinson Cancer Center, USA) also tracked virus-specific CD8$^+$ T cells in virus-driven cancers — such as Epstein-Barr virus-specific T cells in nasopharyngeal carcinoma and Merkel cell polyomavirus-specific T cells in Merkel cell carcinoma — and reported that these T cells were clinically important. Ming Li (Memorial Sloan Kettering Cancer Center, USA) highlighted tumor-associated macrophages that act as antigen-presenting cells driving CD8$^+$ T cell exhaustion by an IRF8-dependent mechanism[3].

Other speakers reported studies of exhausted CD8$^+$ T cells in other diseases. Se Jin Im (Sungkyunkwan University, South Korea) found that CD8$^+$ T cell differentiation in graft-versus-host disease was similar to the differentiation observed during the typical exhaustion process in infection with chronic lymphocytic choriomeningitis virus. Maike Hofmann (University of Freiburg, Germany) presented CD8$^+$ T cell dysfunction during chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV)[4]. HCV-specific CD8$^+$ T cells exhibit typical features of exhaustion in patients with chronic HCV infection, and their function does not completely recover after the infection has been cured. HBV-specific CD8$^+$ T cells also have dysregulated effector functions and share features

with exhausted CD8$^+$ T cells, however, with several molecular peculiarities.

Overall, these findings demonstrate specific molecular mechanisms underlying T cell differentiation and exhaustion, through rigorous analysis of virus-specific T cells in humans, emphasizing their implications in clinical settings.

SARS-CoV-2-specific T cells in the era of COVID-19 endemic transition

During the COVID-19 pandemic, many people experienced breakthrough infections, and the SARS-CoV-2-specific T cell responses after vaccination and breakthrough infection were discussed at the conference. Alessandro Sette (La Jolla Institute for Immunology, USA) and Min Kyung Jung (KVRI, South Korea) independently demonstrated that SARS-CoV-2 vaccination elicits T cell memory that can cross-recognize diverse variants, including Omicron subvariants[5]. They also revealed that breakthrough infection not only boosts T cell responses against conserved epitopes but also elicits new variant-specific T cell responses. In particular, Jung emphasized that breakthrough infection by early Omicron subvariants elicits CD8$^+$ T cell responses that can cross-recognize later Omicron subvariants.

Speakers also reported memory T cell differentiation after SARS-CoV-2 infection. Onur Boyman (University of Zurich, Switzerland) tracked SARS-CoV-2-specific CD8$^+$ T cells from the acute phase of the disease to one-year follow-up, and reported phenotypes and gene signatures of long-lived memory CD8$^+$ T cells such as the CD45RA$^+$ effector memory phenotype and interferon signaling signature[6]. Antonio Bertoletti (Duke-NUS Medical School, Singapore) reported the presence of SARS-CoV-2-specific nasal-resident T cells after breakthrough infection, which can provide a rapid response in the upper airway upon re-exposure.

Hideki Ueno (Kyoto University, Japan) shared his research on the immunological mechanisms underlying long COVID. More than 2,700 individuals with long COVID were analyzed, and long COVID was divided into three major subgroups based on clinical symptoms. Immunological analysis revealed that each subgroup displays unique types of SARS-CoV-2-specific T cells with a distinct gender difference and suggested the involvement of SARS-CoV-2-specific regulatory T cells in the pathogenesis of long COVID.

Bertoletti also discussed strong T cell responses against SARS-CoV-2 accessory proteins that are synthesized during the early stage of virus replication in asymptomatic individuals living in rural regions of Kenya[7]. He hypothesized that early T cell responses against accessory proteins may lead to abortive infection. This finding is reminiscent of a previous report showing that pre-existing polymerase-specific T cells are associated with abortive SARS-CoV-2 infection, although the dominant T cell antigens differed[8]. Knowledge of the SARS-CoV-2 proteins associated with abortive infection provides insight that could help in designing new vaccines. With regards to vaccines, Ji Yun Noh (Korea University, South Korea) suggested that T cell vaccines containing the spike protein plus other SARS-CoV-2 antigens could be useful for preventing severe disease in the COVID-19 endemic era. Sette also proposed new vaccines including T cell antigens that are broadly conserved across multiple viruses of pandemic interest.

Together, these findings reaffirm the beneficial role of T cells in controlling SARS-CoV-2 infection, and offer crucial insights to support the development of next-generation COVID-19 vaccines.

NK-like activity of CD8$^+$ T cells

Speakers also reported non-canonical activity of memory CD8$^+$ T cells. Eui-Cheol Shin (KVRI and KAIST, South Korea) described the T cell receptor (TCR)-independent IL-15-induced activation of bystander memory CD8$^+$ T cells, and their role in immunopathologic tissue injury, which had been previously reported in individuals with acute hepatitis A[9]. IL-15-activated bystander CD8$^+$ T cells exert natural killer (NK)-like cytotoxic activity, triggered by NKG2D, which is upregulated by IL-15. However, concurrent TCR signals counteract the IL-15-induced NK-like cytotoxic features of bystander CD8$^+$ T cells, including NKG2D upregulation. With regards to this mechanism, a gene signature has been elaborately defined and validated, which is specifically upregulated in TCR-independent IL-15-induced bystander activation. It is expected that this bystander activation-specific gene signature will be useful for investigating whether bystander T cell activation is involved in the pathogenesis of other viral diseases and chronic inflammatory diseases. Su-Hyung Park (KAIST, South Korea) also reported TCR-independent cytokine-induced activation of CD8$^+$ T cells, and their NK-like cytotoxic activity, in a model of alopecia areata. Virtual memory CD8$^+$ T cells activated by IL-12, IL-15 and IL-18 exert NKG2D-dependent innate-like cytotoxicity, and contribute to the pathogenesis of the disease[10].

Arne Akbar (University College London, UK) highlighted NK-like functions of senescent CD8$^+$ T cells, and reported that sestrins are responsible for upregulation of NKG2D in senescent CD8$^+$ T cells and their NK-like cytotoxic activity[11]. This finding is in line with the IL-15 hyper-responsiveness of senescent CD8$^+$ T cells to acquire NK-like cytotoxicity, which was reported by Shin. It has been proposed that NK-like activity of senescent CD8$^+$ T cells may provide broad protection against infection and malignancy, as well as cause immunopathology in inflammatory conditions.

Efforts to get closer to the human immune system

A keyword in current biomedical research is 'translation' from basic research to the clinic, which is also a focus in immunological research. Therefore, the conference presentations included many studies of patients' specimens and analyses of disease cohorts. However, such immunological studies have limitations because we cannot easily test hypotheses in human patients, as emphasized by Mark Davis (Stanford University, USA) in his plenary lecture. As a tool to overcome this limitation, Davis presented his experience with organoids of human secondary lymphoid organs[12]. Immune organoids derived from human tonsils or spleens can recapitulate human adaptive immune responses in various contexts. Applying gene-editing technology to immune organoids enables us to test hypotheses and reveal mechanisms in human systems. Moreover, combining immune organoids with peripheral tissues allows the recapitulation of immune–tissue interactions.

Another approach for improving translational immunology was presented by Barbara Rehermann (NIDDK, National Institutes of Health, USA) who introduced mice containing wild-type microbiota[13]. This model was developed to overcome the limitations of laboratory mice lacking host–microorganism interactions that are physiologically important and present in the natural world. In preclinical studies, mice with wild-type microbiota mimic human immune responses better than conventional laboratory mice, demonstrating their usefulness in translational immunology. David Masopust (University of Minnesota, USA) presented another ingenious biological workaround, aimed at optimizing the use of laboratory mice. Through iterative T cell transfer and boosting, memory CD8$^+$ T cells underwent around 50 cumulative successive immunizations over 10 years, far exceeding the mouse lifespan[14]. This model

enables us to explore T cells with enduring functional capabilities that persist for many years beyond the organism's lifespan.

Advanced computational approaches can also robustly improve studies of human immunology. Paul Thomas (St Jude Children's Research Hospital, USA) described how the antigen specificity of TCR can be decoded using a 'reverse epitope' approach[15]. For example, longitudinal tracking of TCR sequences during SARS-CoV-2 infection provides repertoire-scale information about the magnitude, specificity, phenotype and cross-reactivity of T cell responses. This approach is expected to be useful for understanding the structure and role of the T cell repertoire in diverse pathological conditions.

Future steps

The COVID-19 pandemic led us to realize our information gaps about human immunology, despite great progress in 'mouse immunology' during the past several decades. To bridge this knowledge gap, we must leverage the insight and techniques obtained from immunological research in mouse models, as well as apply the innovative approaches that were discussed at this year's conference, to substantially improve our understanding of human immunology. Human immunology can teach us about human-specific mechanisms and about what a mammalian immune system looks like in the real world, as described by Davis in his lecture.

In the future, the immunology series of the conference will focus on innate and adaptive immune responses against viruses and tumors. A major topic will be how we can investigate deep mechanisms and test hypotheses in human immunological studies. For example, cause-and-result relationships can be demonstrated by studying patients treated with biological blockers that target specific cytokines, ligands or receptors. In addition, molecular mechanisms can be revealed by investigating viral infections in patients with inborn errors of immunity. Moreover, the clinical importance of findings from basic immunological studies can be verified by analyzing large clinical databases, such as nationwide cohort databases. By sharing research experiences and promoting discussions, the conference on 'Infection and Immunity' aims to serve as an agora for building up high-standard human immunology, and promoting the translation of basic immunology to clinics.

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Competing interests

The authors declare no competing interests.