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Cytokines 2017 in Kanazawa: Looking beyond the horizon of integrated cytokine research from the sea of Japan

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ABSTRACT

At the 5th Annual meeting of the International Cytokine and Interferon Society held in Kanazawa, Japan from Oct. 29–Nov. 2 2017, new research was presented in the broad field of cytokine and interferon research. The meeting provided an outstanding platform for investigators in basic science and clinical research to communicate, share and discuss their recent findings in this fast moving area of research.

1. Introduction

The field of cytokine and interferon research has been moving at an unprecedented rate over the last years and, amongst other major breakthroughs, has witnessed the identification of novel cell death mechanisms, the discovery of innate lymphoid cells, the elucidation of the impact of microbiota on the immune system, the discovery of debilitating auto-inflammatory diseases caused by aberrant activation of the inflammatory response, and so on. The 5th Annual Meeting of the International Cytokine and Interferon Society entitled "Looking beyond the horizon of integrated cytokine research" held in Kanazawa, Japan, Oct.29-Nov. 2 2017 offered a unique and outstanding networking environment for investigators to present their most recent findings in the field of cytokine research. A major focus was given to the role of cytokines in infection, cancer, and autoimmunity, as well as the development of therapeutic interventions. Altogether, beautiful weather, wonderful Japanese hospitality, and the scenic Japanese Alps provided the more than 800 participants with a high-quality conference and a fantastic Japanese autumn experience in the beautiful castle town of Kanazawa (see Fig. 1. Photos taken by D. Olagnier).

2. Opening keynote lectures

The main theme of this year meeting was: "Looking beyond the horizon of integrated cytokine, interferon and chemokine research". In that spirit, the keynote speakers of the meeting were Tadamitsu Kishimoto (Osaka University, Japan), Richard Flavell (Yale University, USA), and Nancy Reich (Stony Brook University, USA) who gave an overview of their past and present research covering the main topics of this 2017 Cytokine meeting. The first keynote speaker was Tadamitsu Kishimoto (Osaka University, Japan), the internationally recognized immunologist, who has made major contributions to cytokine research, particularly concerning the function and regulation of the pro-inflammatory cytokine IL-6 [1,2]. Over the years, his research has contributed to the development of anti-IL-6 receptor therapy for several immune disorders [1,2]. Amongst the major scientific honors and awards received during a carrier that has spanned more than 40 years, Dr. Kishimoto was recently listed by the Institute for Scientific Information (ISI) as one of the world's most influential scientists, belonging in the prestigious top 10H-index ranking of active biologists. During his presentation, Dr. Kishimoto discussed previously published studies describing the role of Arid5a as a key regulator of inflammation. Arid5a was initially identified as a unique RNA binding protein that stabilizes IL-6, but not TNF-α mRNA, through binding to the 3′ untranslated region of IL-6 mRNA. Arid5a is a nuclear protein that is translocated to the cytoplasm in response to inflammatory stimuli, where it competes with the ribonuclease Regnase-1 in the maintenance of IL-6 mRNA stability [3]. Arid5a deficiency suppressed IL-6 release in response to LPS treatment but, most importantly, interfered with the development of Th17 cells in experimental autoimmune encephalomyelitis [3]. Interestingly, Arid5a not only bound to the 3′UTR region of IL-6 mRNA, but also to STAT3 and T-bet mRNA in Th17 cells and Th1 cells, respectively [4,5]. Through its capacity to modulate the mRNA stability of these critical inflammatory transcription factors,

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Fig. 1. Views of Kanazawa, Japan. Photos: D. Olagnier.

Arid5a governed Th17 cell differentiation and exacerbated IFNγ-driven sceptic shock [4,5].

The second keynote speaker was the equally prestigious Dr. Richard Flavell (Yale University, USA) whose research has contributed to > 1000 scientific manuscripts. Amongst his many scientific contributions in the field of immunology and molecular biology, Dr. Flavell has recently contributed to our understanding of the homeostatic control of the intestinal microbiome by the inflammasome, a topic that has been extensively reviewed by this group [6,7]. Recently, Flavell and colleagues identified Nlrp9b as a host restriction factor for rotavirus infection in the intestine. Nlrp9b is expressed specifically in intestinal epithelial cells, and functions by recognizing double-stranded viral RNA stretches *via* the RNA helicase DHX9; the ribonucleoprotein complex then forms an inflammasome complex with the adaptor protein Asc and caspase-1, leading to the release of the pro-inflammatory cytokine IL-18 and the induction of a gasdermin-D-dependent pyroptotic process [8]. Using genetically engineered mice lacking Nlrp9b specifically in intestinal epithelial cells, Dr. Flavell and colleagues observed an increased susceptibility to rotavirus infection, testifying to the critical role Nlrp9b plays in protection against rotavirus infection. Mice lacking gasdermin-D had a similar sensitivity to infection as Nlrp9b deficient mice. Surprisingly, IL-18 deficient animals had similar symptoms to their wild-type counterparts, therefore demonstrating that gasdermin-D-dependent pyroptosis was the critical Nlrp9b-dependent process accounting for rotavirus restriction *in vivo* [8].

The last speaker of this keynote session was Dr. Nancy Reich (Stony Brook University, USA), a long time leader in the field of cytokine signalling and the incoming President of ICIS, who discussed the dichotomous role of transcription factor STAT3 in cancer development. While some studies demonstrate an intrinsic requirement for STAT3 in the development of cancer of the liver, pancreas, skin, colon and stomach, other studies argue for a suppressive role of STAT3 in cancer establishment [9,10]. Using a model of oncogenic KRAS G12D expression in mouse lung and pancreatic epithelial cells, Reich's lab sought to identify the molecular mechanism(s) underlying the differential role(s) of STAT3 in cancer initiation. A previously unappreciated role for STAT3 was identified in the maintenance of epithelial cell identity and differentiation, a function that was controlled by post-translational modification of STAT3. Whereas the loss of STAT3 expression was associated with the acquisition of a mesenchymal-like phenotype, the continuous phosphorylation of STAT3 on Tyr705 led to a more differentiated epithelial morphology. This novel study highlights the controversial role of STAT3 in cancer development and further indicates that the STAT3 signalling axis may be a target for therapeutic intervention.

3. The burgeoning world of immunometabolism

Luke O'Neill (Trinity College Dublin, United Kingdom) reminded us of our undergraduate biochemistry classes and ancient memories of the Krebs cycle, in a captivating presentation on the increasingly fascinating role of metabolic pathways in the control of the innate immune response. Metabolic reprogramming during activation of immune cells by microbial infection or pattern associated molecular pattern (PAMP) recognition has recently become an area of research described by Dr. O'Neill as "the burgeoning world of immunometabolism".

To go back more than a century, Otto Warburg described the biochemical reaction that bears his name, the Warburg effect, as a mechanism used by tumor cells to increase energy production and facilitate proliferation. Warburg believed that only cancer cells induced a mitochondrial metabolic remodelling from oxidative phosphorylation to glycolysis, as an adaptive response to the increased energy requirements of cancer cell growth. However, it is now recognized that immune cells, such as LPS-stimulated macrophages, induce metabolic remodelling from oxidative phosphorylation to glycolysis as a strategy to regulate the inflammatory response [11–13]. The Warburg effect is a

key feature of inflammation and IL-1β production, a cytokine released downstream of the inflammasome cascade. In the first part of his presentation, Dr. O'Neill returned to earlier studies on the role of the metabolite succinate in the control of the inflammatory response published in *Nature* in 2013 [14]. Dr. O'Neill's group demonstrated that glycolysis was necessary for LPS-induced IL-1β release, but not TNF-α secretion, in murine macrophages. LPS treatment increased the levels of the tricarboxylic-acid cycle (TCA) intermediate succinate and induced IL-1β release through the stabilization of HIF-1α. A complementary study by the same group subsequently demonstrated that murine macrophages shifted ATP production from oxidative phosphorylation to glycolysis upon LPS stimulation, at the same time increasing succinate production [15]. A combination of increased succinate oxidation by the TCA enzyme succinate dehydrogenase (SDH) and an elevation of mitochondrial membrane polarization generated a pro-inflammatory gene signature in LPS-stimulated cells [15]. Interestingly, blocking of succinate oxidation by the dimethyl malonate (DMM) or suppressing mitochondrial ROS production, reversed the LPS-induced inflammatory phenotype [15].

Another Kreb's cycle metabolite itaconate, which is derived from citrate metabolism, was shown recently to regulate inflammation by inhibiting succinate-dehydrogenase-mediated oxidation of succinate [16]. With the presentation of unpublished data, Dr. O'Neill demonstrated that itaconate production was increased in mouse and human LPS-stimulated macrophages. Interestingly, itaconate decreased LPS-induced IL-β release, HIF-1α expression and intracellular ROS accumulation. Mechanistically, itaconate was shown to supress inflammation through the induction of the antioxidant transcription factor Nrf2. Itaconate production resulted in a direct interaction with the cytosolic Nrf2 repressor Keap1, resulting in release and stabilization of Nrf2 that translocated to the nucleus. Nrf2 bound to the promoter proximal regions of inflammatory genes and repressed their transcriptional activity. Altogether, this "renaissance of the Krebs cycle" and its link with the regulation of inflammatory cytokine production argues that metabolic compounds point to new therapeutic interventions for incurable inflammatory-associated diseases.

Coming from O'Neill laboratory, Silvia Galvan-Pena (Trinity College Dublin, United Kingdom) reported a novel metabolic post-translational modification, the malonylation, controlling the inflammatory cytokine production through the modulation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity. GAPDH is mostly known for its role as a glycolytic enzyme and has been used for years as an endogenous control of qPCR or immunoblotting experiments. Much less is known about its possible function as a regulator of the inflammatory response. Whit the blossoming era of immunometabolism, Silvia Galvan-Pena evaluated the possible impact of malonylation of proteins as a way to regulate inflammatory response. First, malonylation of proteins was shown to be induced following macrophage activation. Using mass spectrometry analysis, she showed that amongst other proteins, GAPDH could be malonylated after LPS stimulation in macrophages. Interestingly, GAPDH glycolytic activity was shown to be required for the production of inflammatory cytokines like TNF-α, IL-6 or IL-1β. In the case of TNF-α, the need of GAPDH went beyond its glycolytic activity as GAPDH could also bind TNF-α mRNA and suppress their translation. Altogether, this promising study identified malonylation as a novel post-translational modification affecting GAPDH activity in LPS-stimulated macrophages and suggested that GAPDH could act as a critical regulator of the inflammatory response.

The theory of self and non-self discrimination by the immune system was first introduced by Sir Franck Macfarlane Burnett in a monograph published in 1949. This idea, later demonstrated by Peter Medawar, was the revolutionary concept for which both Burnet and Medawar were recipients of the Nobel prize in 1960. In 1989, the late Charles Janeway posited a new theory, called the infectious Non-Self Model, in which pattern recognition receptors (PRR) expressed by host cells could recognize evolutionarily conserved molecular patterns expressed by pathogens only. Five years later, Polly Matzinger suggested a mind-blowing immunological model in which the immune system does not distinguish between self and non-self, but rather between things that may cause damage to the host and things that would not create damage. This theory, the so-called danger model, still stands within the scientific community as the theory of how the immune system functions. This brief historical background introduces the work presented by Sho Yamasaki (Osaka University, Japan) who discussed research concerning the macrophage inducible C-type lectin receptor (Mincle) that senses damaged cells [17]. In an attempt to elucidate glycolipids ligands derived from damaged cells that are recognized by Mincle, Yamasaki and colleagues fractionated supernatants from damaged cells and identified the intracellular metabolite β-glucosylceramide (GlcCer) as a ligand for Mincle [18]. Cells lacking Mincle receptor were unable to produce inflammatory cytokines in response to synthetic β-GlcCer. Furthermore, genetic depletion of the degrading enzyme of β-GlcCer, GBA1 exacerbated cell death-induced inflammation. Interestingly, this increased inflammation in absence of GBA1 was reduced in animals lacking Mincle [18]. Altogether, Yamasaki and his crew demonstrated that the cell death-derived metabolite β-GlcCer is an endogenous ligand for the immunostimulatory Mincle receptor. This study further illustrates the implications of the Danger model, where only elements that are potentially harmful to the host are detected by the immune system – in this case, an endogenous metabolite-derived from dead/dying cells.

4. Novel insights in antifungal immunity

As described above, the C-type lectin receptor (CLR) like Mincle has been shown to detect and respond to a wide range of molecular patterns including β-glucosylceramide [18]. However, the primary identification of Mincle as a PRR was based on its capacity to shape the immune response to fungal pathogens. Gordon Brown and colleagues (University of Aberdeen, United Kingdom) have contributed substantially to our knowledge of the innate immune detection of fungal pathogens by CLR including the mannose-receptor, Dectin-1, DC-SIGN, or SIGN-R1 [19–21]. During the conference, Dr. Brown reviewed the discovery of a new CLR with a role in antifungal immunity: MelLEC. Unexpectedly, MelLEC did not recognize carbohydrates like other CLR, but rather recognized fungal melanin and more specifically dihydroxynaphtalene (DHN)-melanin. Using polychromatic flow cytometry, the group demonstrated that MelLEC was highly expressed in the lungs and especially in non-myeloid $CD45^-$ cells. In mice, MelLEC was expressed both on $CD45^+$ $CD31^+$ $EpCam^+$ and $CD45^+$ $CD31^+$ $EpCam^-$ cells. Using a knock-out approach in mice, Gordon Brown showed that MelLEC was required for the early inflammatory response to *Aspergillus fumigatus* and more specifically to melanised *Aspergillus*. A final series of experiments performed in human cells convincingly demonstrated that MelLEC was a unique CLR required to control invasive *A. fumigatus* infection.

Sialic acid-binding immunoglobulin-type lectins (Siglec) are cell surface proteins expressed predominantly on immune cells that bind sialic acid and regulate host immune signalling through intracytoplasmic ITIM sequence. Using a GFP reporter cell line, Yasunobu Miyake (Saga university, Japan) identified *Trichophyton mentagrophytes* as a fungal pathogen engaging Siglec. Although immunocompromised patients are the most susceptible to this fungus, *Trichophyton mentagrophytes* can also affect healthy individuals where it causes ringworm or athlete's foot. Miyake speculated that *Trichophyton mentagrophytes* can evade the immune response through the engagement with Siglec, and showed that *T. mentagrophytes* preferentially bound to Siglec-5 and Siglec-9 and more moderately to Siglec-3. Upon engagement with Siglec, the tyrosine phosphatase SHP-1 but not SHP-2 was recruited to the ITIM sequence, thus impairing the production of TNF-α. Surprisingly, sialidase treatment of the pathogen had no effect on the recognition with Siglec, suggesting that the ligand was distinct from sialic acid. The group is now investigating the chemical nature of the

ligand engaged by Siglec to further understand potential novel therapies against this pathogen.

In addition to the involvement of CLR in the defence against opportunistic fungi, the IL-17 family of cytokines are also importantly involved in the anti-fungal immune response [22–24]. Shinobu Saijo and colleagues at Chiba University in Japan developed a murine model of epicutaneous candidiasis, and observed a severe skin inflammation and a high fungal burden in IL-17a and IL-17f knock out animals compared to wild type mice. Infected IL-17 deficient mice contained a lower number of neutrophils, resulting in reduced killing activity against *C. albicans in vitro*. Interestingly, TLR2, Dectin-1, Dectin-2, MyD88, FcγR and Card9 were all dispensable for the clearance of *C. albicans* in the skin, thus highlighting the critical role played by IL-17 and neutrophils in fungal cutaneous defence.

5. What's up in the flavivirus world?

The *Flaviviridae* family of RNA viruses includes among other human pathogens – West Nile virus, dengue virus, tick-borne encephalitis virus, yellow fever virus, Zika virus and several other viruses which cause encephalitis. The vast majority of these viruses are transmitted by the bite from an infected arthropod and hence, classified as arboviruses. Although most of these flavivrus infections are incidental in humans, this group of viruses has been in the spotlights in recent years, particularly as a result of the 2015–2016 Zika virus epidemic. A number of presentations in Kanazawa offered new complementary information about pathogenesis and immune response in the Flavivirus field. Kathryn McGuckin Wuertz (University of Washington, USA) and members of the Michael Gale Jr. group revealed a role for the cGAS-STING antiviral axis in the control of West Nile Virus infection, and demonstrated increased morbidity and mortality with prolonged neurological symptoms in cGAS and STING knockout mice compared to their wild type counterparts. STING deficient animals had increased mononuclear cell infiltration, increased neuronal cell death and lesions in the central nervous system. *In vivo* analyses revealed that cGAS and STING knock-out mice had impaired CD8 T cell responses that correlated with increased viral load in the central nervous system. Sebastian Aguirre from the Fernandez-Sesma laboratory (Icahn School of Medicine at Mount Sinai, USA), who was not present at the conference, recently published a study describing how the DNA sensor cGAS is involved in the early detection of misplaced mitochondrial DNA following DENV infection in monocyte-derived dendritic cells [25,26]. Altogether these studies shed light on the existing cross-talk between the antiviral cGAS-STING pathway and the detection and control of RNA virus infection.

The C-type lectin receptor CLEC5A, also known as MDL-1, is a Syk-coupled C-type lectin receptor that was characterized as a 'driver' of dengue virus (DENV) associated-disease, in part through the release of inflammatory cytokines such as IL-1β [27,28]. CLEC5A was also shown to engage DENV viral proteins and activate the anti-oxidant transcription factor Nrf2 to promote the release of TNF-α [29], suggesting that blockade of CLEC5A may be an interesting therapeutic target to attenuate dengue-induced haemorrhagic shock and lethality in mice. In support of this idea, Shie-Liang Hsieh (Genomics Research Center, Taipei, Taiwan) demonstrated that dengue virus activates platelets *via* another CLR, CLEC2. Activation of platelets through CLEC2 engagement led to the formation of neutrophil extracellular traps (NET) and pro-inflammatory cytokine release through the co-stimulation of TLR2 and CLEC5A. An increase in vascular permeability and a decrease in platelet count were observed in *in vitro* co-culture assays of DENV-infected platelets and neutrophils. Furthermore, blockade of either TLR2 or CLEC5A using antagonistic-antibody treatment attenuated thrombocytopenia and rescued animals from DENV-induced lethality. These observations identify both CLEC2 and CLEC5A as major components in DENV-induced NETs formation and suggest these CLRs as novel therapeutic options in DENV-induced haemorrhagic shock.

Prior to the outbreak of 2015–2016, Zika virus was considered a mild alphavirus infection, with most cases appearing to be asymptomatic. However, early in 2016, the World Health Organization declared the Zika outbreak an international health concern, after scientific evidence linked virus infection with severe birth defects and neurological disorders. The mode of transmission of the virus was also atypical, compared to other viruses in this group, since Zika could transmit from an infected pregnant woman to her foetus, or could be sexually transmitted from an infected adult to another. As a consequence of its rapid re-emergence and its deleterious health-related consequences, Zika-related research grew at an unprecedented rate, with major contributions from the group of Michael Diamond (Washington University, St. Louis) [30–34]. Here, the work of Mithun Das et al. (La Trobe University, Australia) evaluated the antiviral cytokine profile of astrocytes responding to various Zika virus strains. Human astrocytes infected with the original African strain (MR766) or an Asian lineage-derived American strain (PRVABC59) were analysed for their capacity to control and respond to different viruses. This study demonstrated a lack of control of MR766 in human astrocytes despite high type I IFN response and antiviral gene expression. Conversely, restriction of PRVABC59 strain in astrocytes occurred rapidly after infection, and independently of the establishment of a type I IFN response. Although more work is needed to refine the overall antiviral cytokine profile in Zika virus-infected astrocytes, this report enriches our understanding of Zika virus pathogenesis and shows the complexity between type I IFN expression and control of virus replication in human cells.

6. Genetic disorders in cytokine and inflammation regulation

The cGAS–STING and RIG-I/MDA5–MAVS pathways are critical antiviral pathways that recognize and respond to incoming viral DNA and RNA, respectively [35,36]. Type I IFNs (IFN-α and -β) are central cytokines to immune-protection against viral infections but have also been described as potential drivers of immunopathology [37,38]. Emerging alongside the mechanistic details of sensing and response by these crucial pathways, other studies are also characterizing the harmful aspects of unregulated cGAS-STING and RIG-I-like signalling. A significant section of the conference was dedicated to genetic disorders affecting these critical regulatory proteins, and the consequences on cytokine and inflammation regulation in autoimmune and inflammatory disorders. MDA5, a double-stranded RNA sensor, has recently been reported to drive autoimmune diseases [39,40]. Takashi Fujita (Kyoto University, Japan) reported that a missense mutation (G821S) affecting the *IFIH1* gene encoding MDA5 resulted in the development of lupus-like nephritis. Interestingly, lupus-like pathogenesis was dependent on the G821S MDA5 mutation and IFNAR deficiency only partially rescued the symptoms, indicating the involvement of other NF-κB-driven cytokines in disease development. The same missense mutation was also reported in patients with systemic lupus erythematosus, Aicardi-Goutières syndrome and Singleton-Merten syndrome. From Dr. Fujita's laboratory, Shota Shimizu (Kyoto University, Japan) provided insight into the mechanism of action of the *IFIH1* missense mutation and the lupus-like nephritis in mice. Using conditional knock-in mice expressing the MDA5 G821S in different tissues, the group reported that CD11c knock-in mice survived more than six months with lupus-like nephritis. These results interestingly demonstrated that MDA5 G821S mutation in CD11c-expressing DCs is sufficient to induce lupus-like nephritis in mice and that DCs expressing the MDA5 G821S mutation are a target of choice for lupus patients. Hideo Onizawa (Kyoto University, Japan) reported on the development of

spontaneous encephalitis in mutant animals with a gain-of-function mutation of MDA5. This gain-of-function mutation in MDA5 is associated with a genetic disorder characterized by the infancy-onset inflammatory encephalopathy Aicardi-Goutières syndrome (AGS). Mutated animals displayed high level expression of type I IFN in the brain with no lymphocyte infiltration. MAVS-dependent microgliosis was visualized by flow cytometry analyses in the whole brain of the MDA5 mutated mice, indicating that type I IFN production and microgliosis are both implicated in the development of the Aicardi-Goutières-like syndrome in mice.

AGS can also be caused by mutations in other genes affecting nucleotide metabolism including *ADAR1*. In mice, *ADAR1* mutations are embryonically lethal but animals can be rescued by mutating *MAVS* of *IFIH1* genes. In new studies, Robert H. Silverman (Cleveland Clinic, USA) sought to identify which proteins were responsible for the deleterious effects produced by the *ADAR1* mutation. Using a CRISPR/Cas9 ablation approach that targeted the *RNASEL* gene, Dr. Silverman's group was able to rescue the lethality of *ADAR1* mutation in human lung epithelial cells [41]. He also reported that a small molecule inhibitor of the RNase L activity rescued *ADAR1* deficient cells from death. Altogether, the studies from the Fujita and Silverman laboratories offer the potential of novel therapeutic options for patients suffering from debilitating autoimmune and autoinflammatory diseases associated with mutations in *ADAR* or *MDA5* genes.

Koji Yasutomo (Tokushima university, Japan) returned to his studies from a couple of years ago that described a mutation in *NLRC4* leading to familial cold autoinflammatory syndrome (FCAS), a disease characterized by intermittent episodes of rash, arthralgia, and fever after exposure to cold stimuli [42]. The group identified a missense mutation in the NLRC4 gene of patients with FCAS, and was shown to facilitate the formation of NLRC4-containing inflammasomes, leading to caspase-1 cleavage and increased IL-1β production. Transgenic mice expressing the mutated version of *NLRC4* developed dermatitis and arthritis in an IL-1β-dependent manner. Kate Lawlor from the group of James Vince (University of Melbourne, Australia) also reported some of her recently published work on the molecular details underlying why X-linked Inhibitor of Apoptosis (XIAP)-deficient patients exhibit symptoms reminiscent of patients with constitutively active inflammasome [43]. In the absence of XIAP, TLR engagement activated a cell death pathway dependent on IL-1β release following RIPK3 and caspase 8 activation. Dr. Lawlor and colleagues then investigated the mechanism of how XIAP suppressed cell death; with XIAP deficiency, engagement of the TLR-MyD88 axis drove cIAP1-TRAF2 degradation to facilitate TLR or TNFR1 activation of RIPK3-caspase-8 activation and release of IL-1β. This mechanism helps to explain why XIAP-deficient patients are predisposed to hyperinflammation, with symptoms close to those observed with activating inflammasome mutations.

7. Altering mRNA stability as a new way of controlling infection and inflammation

Tight regulation of immune response gene is a critical process, necessary for the maintenance of cellular homeostasis and for the control of disorders related to inflammatory reactions. While transcriptional regulation of inflammatory gene expression has been well characterized in the recent past, it is becoming clear that maintenance and modulation of mRNA stability can also contribute to major changes in the mRNA content of inflammatory cells. Shizuo Akira (Osaka University, Japan) returned to the studies from his group on the endoribonuclease Regnase-1, encoded by the *ZC3H12A* gene, which is involved is the mRNA destabilization of a number of inflammatory genes, including IL-6, IL-12, etc [44,45]. Regnase-1 is expressed in unstimulated cells and levels decrease following TLR engagement through an IKK-dependent proteasomal degradation pathway. Therefore, Regnase-1 acts as a potent brake of the inflammatory response by destabilizing inflammatory gene mRNA. Studies presented by Osamu Takeuchi (Kyoto University) corroborated the studies from the Akira group, and demonstrated the involvement of Regnase-1 in the alteration of inflammatory mRNA stability in the control of immune responses [46,47]. Dr. Takeuchi also reported the effect of another RNA-binding protein (RBP) – Roquin. By recognizing stem-loop structures in mRNA encoding inflammatory proteins, Roquin licenses a subset of inflammatory gene mRNAs for degradation by recruiting a CCR4-NOT deadenylase complex to target mRNAs. Animals lacking Roquin spontaneously developed autoimmune symptoms, including enhanced release of TNF-α in immune cells. Mechanistically, both Regnase-1 and Roquin regulated an overlapping set of mRNAs, but functioned in distinct subcellular compartments. Yoshinari Nakatsuka (Kyoto University) from the Takeuchi laboratory expanded on this theme and demonstrated that Regnase-1 degradation in pathogen-sensing airway epithelial cells is critical for the induction of antibacterial immunity. In lung cells, Regnase-1 was quickly degraded following infection with *P. aeruginosa* or stimulation with TLR ligands. In the lungs of Regnase-1 deficient animals an increased accumulation of neutrophils and high IgA concentrations were observed compared to wild-type mice. Mechanistically, RNAseq analysis revealed that the lack of Regnase-1 in airway epithelial cells altered the expression of a novel set of genes involved in the direct control of pathogen proliferation, thus indicating that Regnase-1 degradation is a critical step in antibacterial control. Overall, the studies provide new insight into the control of inflammatory responses through the destabilization of a critical set of mRNA *via* interactions with ribonucleoprotein complexes.

8. Innate lymphoid cells in focus

Innate lymphoid cells (ILCs) constitute a family of lymphoid cells that do not express rearranged receptors and possess key regulatory functions in innate immunity and tissue remodelling [48,49]. Following along on the theme of immunometabolism, Laurel Monticelli (Cornell University, USA) presented recent studies on how cell-intrinsic metabolic pathways control ILC2 functions [50]. Deletion of Arginine-1 (Arg-1)abrogated type 2 lung inflammation, restrained ILC2 proliferation and restricted cytokine production by disrupting metabolic programming [50]. New results were also presented illustrating that Arg-1 is heterogeneously expressed across all ILC subsets and is dynamically regulated in a tissue specific manner after alterations in the mucosal barrier. Differences in Arg-1 expression delineated distinct ILC1 or ILC3 subpopulations, with specific immune or tissue-repair functions, compared to Arg1 deficient cells from the same lineage. These findings highlight the instructive role of Arginase-1 and its downstream metabolites in the control of ILCs specific tissue function. This link between metabolism and cytokine regulation was strengthened by Yasutaka Motomura, Laboratory for Innate Immune systems (Yokohama, Japan) who reported that the blockage of calcium signalling completely inhibited IL-4 production in ILC2s in a cystenyl leukotriene D4 (LTD4)-dependent manner. Surprisingly, animals deficient in IL-33, a master regulator of ILC2 expansion, lacked the capacity to induce IL-4 through LTD4 in ILC2, thus supporting a synergistic role for LTD4/calcium signalling and IL-33 signalling in the control of IL-4 production in ILC2s. While ILC2s are now widely recognized as major producers of Th2 cytokines, the signalling details controlling ILC2s response are remain poorly defined. Saya Moriyama from the David Artis group (Cornell University, USA) showed that ILC2s selectively express the β2 adrenergic receptor (β2AR) and reside in intestinal tissues close to adrenergic neurons. β2AR-deficiency resulted in dysregulated Th2-dependent ILC2 inflammatory response upon helminth challenge. Conversely, engagement of β2AR using a specific agonist reduced ILC2-

induced response and inflammation *in vivo*. The data presented by Moriyama are the first to provide evidence of a neuronal-driven regulation of ILC2-dependent type 2 inflammation at mucosal sites.

IL-33, a member of the IL-1 superfamily of cytokines, is one of the critical cytokines governing group 2 innate lymphoid cell expansion and function, and may also be involved in chronic inflammatory diseases. Satoshi Takaki (National Center for Global Health and Medicine, Chiba, Japan) previously reported that lung IL-5-producing ILC2s played a critical role in regulating eosinophil biology [51]. Dr. Takaki investigated the consequences of a prolonged IL-33 treatment on the biology of pulmonary arteries [52] and observed a significant expansion of eosinophils and the ILC2 subset, leading to occlusion and hypertrophy of pulmonary arteries. Surprisingly, the pulmonary arteriopathy was rescued in IL-5 or eosinophil-deficient mice, indicating that IL-5-producing ILC2s and eosinophils play pivotal roles in pulmonary arterial hypertrophy.

9. ICIS young investigator award winners: the rising stars of the cytokine field

The 1st place Milstein Young Investigator Award winner Ari B. Molofsky from the laboratory of Richard Lockesley (UCSF, USA) provided a succinct introduction to ILC2s, and then described his recently published studies demonstrating that adipose tissue ILC2s promote adipose tissue function and serve a protective role in models of type 2 diabetes and obesity [53–56]. In adipose and other tissues, IL-33 cytokine is the master regulator controlling ILC2s expansion and function; however the main cells and the exact downstream signalling involved in ILCs control and expansion in tissues are not fully characterized. By using an innovative high-resolution imaging approach, combined with the use of genetically deficient mice, Dr. Molofsky showed that ILC2s are maintained in specific microanatomic tissue niches defined by subsets of non-hematopoietic IL-33-expressing cells. Young Investigator Award winner Christian K. Holm (Aarhus University, Denmark) presented his novel studies on the negative regulation of the antiviral adaptor molecule STING by nitro-fatty acids (NFAs). He showed that NFAs were endogenously produced upon herpes virus challenge *in vivo*, and mechanistically, NFAs covalently bound to STING by nitro-alkylation which was sufficient to suppress STING-induced type I IFN and inflammatory responses. Interestingly, he also demonstrated that NFAs could be used as therapeutic treatments to prevent STING-dependent inflammation in cells from SAVI patients. Susan Carpenter (University of California Santa Cruz, USA), a former fellow of Katherine Fitzgerald at UMass, identified a new long non-coding RNA (lncRNA), called GAPLINC using RNA sequencing data sets from primary human monocytes and human monocyte-differentiated macrophages. GAPLINC was induced from more than a thousand-fold in cells transitioning from monocytes to macrophages; whereas expression of GAPLINC was rapidly reduced upon TLR engagement. GAPLINC knockdown resulted in the up-regulation of multiple inflammatory genes suggesting that GAPLINC lncRNA functioned as a negative feedback regulator of the inflammatory response in primary human cells. Finally, Tatsuma Ban (Yokohama University, Japan), recounted his pubished results, highlighting the role of the Src kinase Lyn in suppression of IRF5 activity and restraining the development of SLE-like disease in mice.

An Honorary Lifetime Award was presented to Dr. Ganes Sen (Lerner Research Institute, Cleveland Clinic, USA) for his many contributions to the field of interferon research. Dr. Sen provided a brief summary of recent and ongoing research which over the years has included studies on the mechanism of Toll-like receptor signalling, particularly the dsRNA sensing TLR3, RIG-I-like helicase receptors and the cytoplasmic DNA-sensing cGAS/STING receptor [57–61]. His studies have also provided groundbreaking insights into the mode of action of a set of IFN-induced antiviral proteins, the IFITs [62–64]. Other studies from the Sen laboratory have revealed a novel role for the IRF-3 transcription factor, demonstrating that upon activation by virus infection, IRF-3 triggered apoptosis by interacting with and transporting the pro-apoptotic protein Bax into mitochondria [65,66]. A long time colleague and friend of many ICIS attendees, it was fitting to see Dr. Sen receive the Honorary Lifetime Award, although he assured everyone that this was not his ‘Sayonara award’.

The outgoing President of ICIS, Dr. Tada Taniguchi is another internationally recognized leader in the cytokine and immunology world with many scientific achievements. Dating back to 1980, Dr. Taniguchi is credited with the first cloning of the beta interferon gene. Two years later, he reported the first cloning of the gene for interleukin 2, and subsequently identified and cloned the first two members of the IRF family of transcription factors. He and his team have provided over the years major contributions to the regulation of the antiviral immune response, interferon gene regulation, T-cell immunity, and molecular signalling. During a presentation as outgoing President, Dr. Taniguchi discussed recent studies on the sensing of nucleic acid by high mobility group protein HMGB1. Selective activation of nucleic acid-sensing cytosolic and Toll-like receptors requires the sensing of nucleic acids by HMGB1. The Taniguchi group characterized an array of HMGB-binding, nonimmunogenic oligodeoxynucleotides (ni-ODNs), and demonstrated that ni-ODNs suppressed the activation of innate immune responses. Subsequently, his group has demonstrated that small RNA coupled with HMGB1 increased the potential for antiviral gene activation and limited viral pathogenesis *in vivo*. These studies lay the groundwork for the development of small RNA therapeutics capable of selectively stimulating the immune response.

10. Concluding remarks

The 5th annual ICIS Conference in Kanazawa was a great success and was able to boast the highest attendance of any ICIS conference, or joint conference from the previous Interferon and Cytokine Societies. Excellent science, beautiful location and wonderful hospitality combined to make this a memorable conference. We look forward to the ICIS Conference in Boston on October 27–30th, 2018.

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Competing financial interests

The authors declare no competing financial interests.

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