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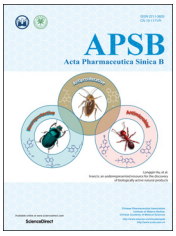

MEETING REPORT

Regulation of immune-related diseases by multiple factors: A meeting report of 2017 International Workshop of the Chinese Academy of Medical Sciences (CAMS) Initiative for Innovative Medicine on Tumor Immunology

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Abstract Immune cells play key roles in cancer and chronic inflammatory disease. A better understanding of the mechanisms and risks will help develop novel target therapies. At the 2017 International Workshop of the Chinese Academy of Medical Sciences Initiative for Innovative Medicine on Tumor Immunology held in Beijing, China, on May 12, 2017, a number of speakers reported new findings and ongoing studies on immune-related diseases such as cancer, fibrotic disease, diabetes, and others. A considerably insightful overview was provided on cancer immunity, tumor microenvironments, and new immunotherapy for cancer. In addition, chronic inflammatory diseases were discussed. These findings may offer new insights into targeted immunotherapy.

1. Introduction

The immune system protects the body against illness and infection. However, an atypical immune response can cause the development of chronic inflammatory diseases including cancer. Understanding the crosstalk between immune cells and disease initiation provides better opportunities for identification of drug targets in the future. This report summarizes the major points presented at the 2017 international workshop on the regulation of immune-related diseases. The International Workshop on Tumor Immunology is sponsored by the Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (CIFMS) to provide a unique opportunity for investigators and scientists to interact with each other. The 2017 International Workshop was held in Beijing, China, on May 12, 2017 and consisted of 7 keynote lectures and 6 short talks. With a focus on the most recent advances in the fields of immune-related diseases, including cancer, fibrotic diseases and obesity, the programs covered a wide range of important topics, including cancer immunotherapy, tumor immunity, cancer metabolism, tumor dormancy, microparticles, and protein-quality control. Some emerging fields, such as oncolytic vaccines and personalized prophylactic cancer vaccines were also included.

2. Session on "cancer immunity" chaired by Dr. Bo Huang

2.1. Plenary lecture on "hot topics and trends in cancer immunotherapy" by Dr. Xuetao Cao

The Scientific Innovation Program for Medical Sciences and Health (SIPMSH) already has been incorporated in the '*Plan of Health China* 2030' from the state council[1]. Dr. Xuetao Cao, the current President of the CAMS[2], elaborated on "hot topics and trends in cancer immunotherapy" by five categories, including personalized tumor vaccines, antigen-specific immunotherapy, predictive immunotherapy biomarkers, blockade of immune checkpoints, and metastasis prevention.

Dr. Cao first discussed the design and application of immunotherapy by individual oncogenomics. With the high efficacy and low cost of deep sequencing, personalized tumor vaccines have been possible for cancer immunotherapy. The mutational spectrum obtained by next-generation sequencing provided valuable information for the design of vaccination peptides, tumor neoantigen identification, etc.[3]. With the necessary adjuvants, modified synthetic peptides targeting a tumor antigen are used as therapeutic vaccines for cancer[4]. Moreover, autologous antigen-presenting cells (APCs) have been introduced with tandem minigenes or synthetic peptides of all mutations. This technology has led to the discovery of some mutations in APC in the context of the autologous major histocompatibility complex (MHC). Adoptive cell therapy by expansion and training of autologous lymphocytes *in vitro* is promising for cancer patients. Cao mentioned that the future of "omics-driven" oncology may have a multiplatform approach that will allow comprehensive characterization of a tumor at multiple levels[3]. He then moved on to antigen-specific immunotherapies, such as chimeric antigen receptor (CAR)-T therapy and dendritic cell vaccines. Improvements in CAR-T cell delivery to tumor cells will further expand the T cell gene therapies. He pointed out the current focus on efficiency enhancement of dendritic cell vaccines. In the latest issue of *Cancer Cell*, Spranger et al.[5] found that effector T cell migration depends on the presence of $CD103^+$ DCs producing CXCL10, and a lack of $CD103^+$ DC-mediated effector T cell recruitment contributes to immune escape. Dr. Cao pointed out that dendritic cells play a critical role in tumor-infiltration by T cells. He initiated the phase I clinical trial in 2001 with the Chinese Food and Drug Administration (CFDA) approval, and spent ten years in the phase II trial from 2002 to investigate the synergistic effects of DC vaccines with chemotherapy for advanced colon cancer patients. Eradication of inhibitory immune factors by chemotherapy enhances the efficiency of DC vaccines. The therapeutic response rate increased from 23% with chemotherapy alone to 45% with chemotherapy plus DC vaccines. He concluded that the repertoire of tumor-infiltrated T cells and their cytokine profiles tightly link with the efficiency of immunotherapy.

Dr. Cao then talked about predictive signature biomarkers in cancer immunotherapy[6]. Currently there are extensive investigations to find biomarkers from tumor surface proteins, the tumor microenvironment, tumor-adjacent tissues and peripheral blood of cancer patients. Mleenik et al.[7] recently reported that the tumor microenvironment and immunoscore are critical determinants of the likelihood of metastasis. Dr. Cao's laboratory also identified a prognosis predictor for the transformation of normal liver to hepatocellular carcinoma (HCC), and an interferon-α (IFN-α) therapeutic predictor for HCC patients[8,9]. High-level HCC cell expression of micro-RNA 199 (miR-199) is associated with less aggressive disease in patients with HCC. miR-199 delivered by AAV8-based gene therapy inhibited HCC growth by blocking PAK4-Raf-MEK-ERK pathway[8]. Although IFN-α therapy is

effective for HCC, the response rate is only about 15% to 20%. Regarding biomarkers for prediction of prognosis and response to interferon-α (IFN-α) therapy in HCC, Dr. Cao's laboratory has discovered that low retinoic acid-inducible gene-I (RIG-I) expression had shorter survival and poorer response to IFN-α therapy. RIG-I deficiency promotes HCC carcinogenesis in mice with gender disparity. RIG-I enhances IFN-α response by amplifying IFN-α effector signaling *via* strengthening STAT1 activation[9].

Dr. Cao then discussed the blockade of immune checkpoints. He encouraged the scientists to have an open mind to discover new checkpoints but not to simply act as a follower in PD1 tides. CTLA-4, PD-1 and PD-L1 are under an extensive investigation with approval applications using monoclonal antibodies. Researchers should pay attention to some new immune checkpoints targets, such as KIR (killer cell Ig-like receptor), LAG-3 (lymphocyte activation gene 3), GITR (glucocorticoid-induced tumor necrosis factor receptor), OX40 (tumor necrosis factor receptor superfamily, member 4) and CD47 (cluster of differentiation 47, integrin associated protein). He noted that PD-1 monotherapy might induce a compensatory inhibitory pathway based on the latest finding from Gao et al.[10]. They evaluated untreated and ipilimumab-treated tumors from patients in a presurgical clinical trial, and identified VISTA as another compensatory inhibitory immune checkpoint in prostate tumors after ipilimumab therapy[10]. Dr. Cao discussed some clinical studies with anti-PD-1 monoclonal antibody therapy[11–16]. Sustained tumor regression with PD-1/PD-L1 blockade varies with many different cancers. The effective rate for Hodgkin's cancer is about 69% to 87%, but the maximum effective rates varied from 19% to 50% for other cancers, including melanoma, lung cancer and liver cancer. This raised the question of resistance to PD-1/PD-L1 blockade for some patients. Indeed, Zaretsky et al.[17] analyzed biopsy samples from paired baseline and relapsing lesions in patients with metastatic melanoma who had an initial objective tumor regression followed by disease progression. They found that JAK2 mutation promotes acquired resistance to PD-1 blockade immunotherapy in patients with melanoma. The resistance was associated with defects in the pathways involved in interferon–receptor signaling and in antigen presentation. IFN-γ released by T cells plays critical roles in the PD-1/PD-L1 blockade therapy. However, there are still some questions about the major roles of IFN-γ on the tumor itself or vessel normalization[18]. Dr. Cao introduced the concept that prolonged interferon signaling activation increases resistance to immune checkpoint blockade by a study from Benci et al.[19] and presented some novel findings from his laboratory to address how interferon acts against tumor by post-translational and epigenetic modification.

In his last topic on metastasis prevention, Dr. Cao began with a review of the four new hallmarks of cancer including genome instability and mutation, avoiding immune destruction, deregulating cellular energetics, and tumor-promoting inflammation[20]. The interaction between tumor cells and host cells includes lymph vessels, cellular matrix, blood vessels, immune cells and fibroblasts, and is one of the leading questions in metastasis prevention. Monotherapy is almost never able to block metastasis. In the future, combined and targeted conventional therapy coupled with immunotherapy might increase the efficacy and sustainable clinical response in cancer patients[21]. As an example, Dr. Depinho's group showed the effectiveness of combinatorial immunotherapy, eradicating myeloid-derived suppressor cells, for castration-resistance prostate cancer[21]. He emphasized the key role of neutrophils in metastasis[22–24]. Dr. Cao ended his lecture by presenting latest study from his laboratory about lung pre-metastatic niche formation by activating alveolar epithelial TLR3 to recruit neutrophils[25]. TLR3-, but not TLR4- or TLR9- deficient mice show reduced lung metastasis in spontaneous metastatic models. Primary tumor-derived exosomal RNAs activate TLR3 in lung epithelial cells, consequently inducing a pre-metastatic niche by chemokine secretion and neutrophil recruitment[25]. Inflammation, angiogenesis and vascular permeability, lymphangiogenesis, immunosuppression, organotropism, and reprogramming play important roles in the formation of the pre-metastatic niche[26].

2.2. Plenary lecture on "metabolic control of immune cell subsets in the tumor microenviroment" by Dr. Weiping Zou

Dr. Zou's laboratory has been studying the cross-talk among immune cell subsets and tumor (stem) cells in the tumor microenvironment for a long time, with a focus on cancer metabolism and T cell immunity[27], immunosuppressive networks and PD-L1/PD-1 blockade[27,28], cancer genetic and epigenetic events, and tumor immunity[29,30]. Dr. Zou started off by emphasizing that the cancer microenvironment holds the key in understanding tumor immunity and therapy. His recent review articles have summarized the latest progress in the immune response and regulation in the human tumor microenvironment[24,31]. He introduced his recent study with a focus on how glycolysis and oxidative stress affect effector T cells in the tumor microenvironment. His group has demonstrated that tumor-associated glycolysis affects the functions of effector T cells *via* an EZH2-H3K27me3-mediated epigenetic regulatory mechanism. Insufficient glucose in the tumor microenvironment causes activation of a glycolytic switch in the effector T cell. High levels of miR-101 and miR-26a reduced levels of EZH2, Notch activation, and T cell survival and poly-functionality. Their finding highlights the metabolic pathways controlling T cell subset functional behavior and affecting cancer immune checkpoint therapy[27]. Next, Dr. Zou introduced the concept of progression for immune imbalances and suppressive networks in the human tumor microenvironment. He is one of pioneers in the study of the mechanisms of inhibitory and stimulatory B7 imbalances in the human cancer microenvironment[28,32,33]. He ended his talk by sharing some thought about mechanisms of inhibitory B7-H1 (PD-L1) in the evasion of T cell-mediated immunity.

3. Session on "tumor microenvironments" chaired by Dr. Zhuowei Hu and Dr. Bo Huang

3.1. Plenary lecture on "cancer: new concepts and strategies" by Dr. Bo Huang

Dr. Huang briefly introduced the background of SIPMSH and mentioned that CIFMS will continue to support research in medical sciences until 2030. Dr. Huang noted several breakthroughs in oncology from several groups[34–36], and then he presented results from his laboratory for tumor dormancy, tumor microparticles and tumor metabolism. First, he pointed out that not only the immune systems but also biomechanical forces can induce tumor (stem) cells into dormancy. Dr. Yuying Liu's results showed that IFN-γ can induce tumor dormancy from IDO1/AhR-dependent pathways[35]. He then shared some thoughts about the role of the interferon signaling pathway and tissue stiffness on tumor dormancy. Next, he pointed out that tumor cell-derived microparticles (T-MPs) can educate local macrophages to M2 type cells, and then promote tumor cell

proliferation, vascular angiogenesis, and an inhibitory immune microenvironment[37]. T-MPs can also train distant immune cells to form a pre-metastatic niche, and promote tumor metastasis. However, T-MPs can change from 'devil' to 'angels'. He showed T-MPs containing anti-tumor drugs such as an oncolytic virus are a novel approach that reverses drug resistance of tumor-repopulating cells (TRCs), T-MPs are great candidates for tumor vaccines and targeted therapy delivery systems[38–40]. In his last topic, Dr. Huang indicated that it is important to understand tumor cells from atypical metabolism. Carbohydrate/glucose metabolism is the most important pathway to provide ATP in human body. Liver cancer cells have atypical glycolysis but active gluconeogenesis. The key gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK, PCK1) is highly expressed in liver, which plays a critical role in gluconeogenesis in both normal and tumor cells[41]. Recent studies also suggest that the mitochondrial isoform of PEPCK (PEPCK-M, PCK2) may be another key regulator of metabolism and survival in cancer cells[42]. Dr. Huang ended his presentation by showing the need for further investigation of metabolic cross-talk between immune cells and tumor cells.

3.2. *Plenary lecture on "chromatin as a mechanosensor in gene expression and mechanobiomedicine" by Dr. Ning Wang*

Mechanical forces play critical roles in the regulation of biological functions of living tissues and organisms in normal physiology and the diseased state. Almost all cells generate and sense mechanical forces. Most cells attach to extracellular matrix (ECM) proteins or other cells *via* specific mechanosensors (*e.g.*, integrins and cadherins) on the cell surface. The forces are focused at focal adhesions, a macromolecular assembly of many proteins and molecules at the cell–ECM interface. These concentrated forces are propagated along the cytoskeleton to various parts of the cytoplasm. However, despite significant efforts for many years, it remains elusive how mechanical forces influence gene expression in living cells.

Dr. Wang pioneered a study in 1993 to show that integrin transfers forces from the cell membrane to the cytoskeleton[43]. In the early 2000s, his laboratory demonstrated the first experimental evidence that the endogenous forces generated by living cells exert pre-stress (cell tension) to stabilize the cytoskeleton and determine cell stiffness[44,45]; later his laboratory demonstrated that forces *via* integrins can directly activate cytoplasmic enzymes at long distances[46]. In 2009, Dr. Wang introduced the concept of mechanomedicine[47] and proposed that an extracellular matrix force applied *via* integrins could directly impact gene expression[48].

Dr. Wang's laboratory recently demonstrated that gene transcription can be upregulated *via* force-induced direct chromatin stretching. Using green fluorescent protein (GFP) to label multiple sites in a chromatin domain and inserting a gene of interest, *DHFR*, between GFP spots, they were able to quantify the degree of chromatin stretching and transcription in a living cell[49]. They found that gene upregulation was dependent on force magnitude, force directionality, and the degree of chromatin stretching as well as tension in the cytoskeleton. Disrupting the force propagating pathway from the cytoplasm to the nuclear lamina abolished force-induced transcription. They discovered two nuclear proteins that transmitted force from nuclear lamins to the chromatin. They show that force-induced transcription does not depend on transport between the cytoplasm and the nucleus. Thus, they have discovered that chromatin is a *bona fide* direct mechanosensor. They highlighted their findings that forces and matrix mechanics regulate stem cell differentiation[50,51] and early embryonic development[52]. They provided evidence of low forces in facilitating growth and metastasis of the malignant, undifferentiated soft TRCs[53]. Furthermore, they found that self-renewal gene *Sox2* is a major player in promoting growth of TRCs and the matrix mechanics-dependent plasticity of TRCs[54]. Dr. Wang revealed that cell deformability is a key factor in the control of extravasation dynamics during cancer metastasis[55]. His findings demonstrate the critical roles of mechanotransduction and mechanobiology in stem cell biology and cancer cell biology[56,57]. Dr. Wang proposed that mechanobiology-based medicine (mechanobiomedicine or mechanomedicine)[58] is poised to emerge as an exciting branch of medicine that uses mechanics-based principles and engineering-based technologies for novel diagnostics and therapeutics of diseases.

3.3. *Short talk on "targeting protein degradation of tumor-promoting factors as a therapeutic strategy of cancer" by Dr. Fang Hua*

Diabetes is a worldwide health problem with severe complications. High insulin/IGF is a biologic link between diabetes and cancers, but the underlying molecular mechanism remains unclear. Dr. Hua started her presentation by introducing the proteostasis network as a drug target for chronic diseases. She previously found that the TRIB3–Smad3 interaction promotes the epithelial-to-mesenchymal transition (EMT) and tumor invasion[59]. She then reported a previously unrecognized tumor-promoting mechanism for stress protein TRIB3, which mediates a reciprocal antagonism between autophagic and proteasomal degradation systems and connects insulin/IGF to malignant promotion. High-level TRIB3 in cancer patients correlates with tumor progression and poor survival rate. Silencing TRIB3 protects against the tumor-promoting actions of insulin/IGF and attenuates tumor initiation, growth and metastasis *in vivo*. The interaction between TRIB3 and autophagic receptor p62 hinders p62 binding to LC3 and ubiquitinated substrates, causes p62 deposition and suppresses autophagic/proteasomal degradation of several tumor-promoting factors. Interrupting the TRB3/p62 interaction by chimeric peptide Pep2-A2 produces potent anti-tumor efficacies against tumor growth and metastasis. Their study opens the possibility of targeting this interaction as a potential novel strategy against cancers with diabetes.

3.4. *Short talk on "blockade of IDO-kynurenine-AhR metabolic circuitry abrogates IFN-induced immunologic dormancy of tumor-repopulating cells" by Dr. Yuying Liu*

Similar with chemotherapy and radiotherapy, immunotherapy can also cause resistance to form TRCs. Dr. Liu used a soft fibrin gels system to investigate interactions with the immune system that may lead TRCs into dormancy[53]. They found that IFN-γ induces TRCs to enter dormancy through an indolamine 2,3-dioxygenase 1 (IDO1)-kynurenine (Kyn)-aryl hydrocarbon receptor (AhR)-p27-dependent pathway. IFN-γ normally triggers differentiated tumor cell apoptosis *via* STAT1. However, in TRCs that highly expressed IDO1 and AhR, IFN-γ activates IDO1/AhR-dependent p27 induction and activates the dormancy program. Targeting IDO/AhR not only abrogates IFN-γ-induced dormancy but also results in enhanced repression of tumor growth by IFN-γ-induced apoptosis of TRCs both *in vitro* and *in vivo*. Their data represent a

novel mechanism of inducing TRC dormancy by IFN-γ, suggesting a potential effective cancer immunotherapy through the combination of IFN-γ and IDO/AhR inhibitors[35].

3.5. *Short talk on "TRIB3 promotes APL progression through stabilization of the oncoprotein PML-RARα and inhibition of p53-mediated senescence" by Dr. Ke Li*

Acute promyelocytic leukemia (APL), M3-type of acute myeloid leukemia (AML), is driven by the oncoprotein PML-RARα, which antagonizes myeloid differentiation and promotes APL-initiating cell self-renewal[60]. Combined all-*trans* retinoic acid (ATRA) with arsenic trioxide (As_2O_3) or chemotherapy dramatically improves the prognosis of APL patients. However, ATRA/arsenic resistance still causes treatment failure in some APL patients. Dr. Li reported that expression of pseudokinase tribble 3 (TRIB3) associates positively with APL progression and therapeutic resistance. The elevated TRIB3 expression promotes APL by interacting with PML-RARα and suppressing its sumoylation, ubiquitylation, and degradation. This represses PML nuclear body assembly, p53-mediated senescence, and cell differentiation, and supports cellular self-renewal. Genetically inhibiting TRIB3 expression or combination of peptide Pep2-S160 disturbing TRIB3/PML-RARα interaction with ATRA/As_2O_3 eradicates APL by accelerating PML-RARα degradation. The study provides insight into APL pathogenesis and a potential therapeutic option against APL.

4. Session on "new immunotherapy for cancer" chaired by Dr. Zhuowei Hu

4.1. *Plenary lecture on "enhancing anti-tumor immunity with oncolytic vaccines" by Dr. Yonghong Wan*

Current immuno-oncological therapeutics includes checkpoint inhibitors, bispecific antibodies, cancer vaccines, oncolytic viruses (OV) and gene-engineered cytotoxic T cells. Although some of these immuno-oncology agents have already generated substantial benefit over the previous standards of care, the majority of patients are still in need of a beneficial next-generation treatment. To address this need, a growing trend in immuno-oncology drug development is the investigation of combination therapies. However, owing to the heterogeneity of solid tumors and their immunosuppressive microenvironment, it is not yet clear which combinations will be most effective. In Dr. Wan's presentation, he discussed the rationale underlying the combination of oncolytic vaccines with other immuno-oncological therapeutics to optimize clinical outcomes[61]. Dr. Wan emphasized the key role of T cells in successful immunotherapy. The quantity, tumor-specific trafficking, activity and specificity of T cells are four key components for immunotherapy. OV vaccine is a therapeutic approach in cancer treatment that utilizes genetically modified viruses that selectively replicate within tumor cells. Dr. Wan provided experimental and clinical evidence that OV vaccines can effectively expand antigen-specific T cells in the periphery and rapidly recruit them into the tumor. He concluded that OV vaccines might represent an ideal platform to combine with checkpoint inhibitors, conventional cancer vaccines, and adoptive T cell therapies including CAR T cells.

4.2. *Plenary lecture on "a novel prophylactic cancer vaccine platform for non-viral malignancies" by Dr. Yaohe Wang*

While prophylactic vaccination strategies have proven effective for cancers in which the etiological agents are characterized infectious pathogens, for most non-viral malignancies these strategies remain elusive. Strategies reliant on presentation of a limited number of known tumor-associated antigens (TAAs) are largely ineffective due to inappropriate antigen choices from a wide repertoire of potential antigens, and failure to mitigate tumor-induced immunosuppression. Development of effective prophylaxis against non-viral cancers remains a significant challenge, largely due to the lack of appropriate tumor antigens and the difficulty in eliciting effective anti-tumor immunity. Induction of personalized tumor cells from healthy somatic cells creates an opportunity for provision of a range of immunogenic and relevant tumor antigens. Dr. Wang's laboratory has developed a VIReST vaccine (virus-infected reprogrammed somatic cell-derived tumor cell) against pancreatic cancer, in which pancreatic tumor cells were derived from normal somatic cells with induced pluripotent stem cell (iPSC) and gene-editing technologies. These cells were infected with replicating oncolytic viruses to promote effective induction of tumor-specific immunity through virus-induced immunogenic cell death mechanisms. Application of VIReST resulted in enhanced anti-tumor immune responses and prolonged survival in a clinically relevant KPC transgenic mouse model, without inducing detectable autoimmunity. Their results provide exciting proof of the concept and a robust technology platform for the development of prophylactic cancer vaccines to prevent non-viral malignancies in at-risk individuals[62].

4.3. *Short talk on "cirmtuzumab, a new tool for cancer-specific treatment" by Dr. Bing Cui*

Cirmtuzumab is a first-in-class humanized monoclonal antibody that binds the extracellular domain of ROR1. ROR1 is an onco-embryonic antigen that is expressed on the neoplastic cells of patients with chronic lymphocytic leukemia (CLL), other B-cell lymphomas, acute leukemias, and many different solid-tumors[63], but not on non-neoplastic post-partum tissues[64]. Dr. Cui presented studies that he carried out as postdoc in Dr. Thomas J. Kipps's laboratory. The expression of ROR1 associates with the epithelial–mesenchymal transition (EMT), and targeting ROR1 with the monoclonal antibody D10 can inhibit triple-negative breast cancer metastasis[65]. Moreover, ROR1 could complex with T-cell leukemia 1 (TCL1) in chronic lymphocytic leukemia (CLL), and accelerate $CD5^+B220^{dull}$ B-cell leukemia expansion in Eμ-TCL1-Tg (TCL1) transgenic mice. Anti-ROR1 antibody D10 caused ROR1 down-modulation, phosphor-AKT reduction and impaired engraftment of ROR1-positive leukemia cells[66]. However, the affinity of mouse monoclonal antibody D10 is not ideal. During the same period that UC-961, a D10-like high-affinity anti-ROR1 antibody, was screened by phage-display technology, Dr. Kipps's laboratory found that human ovarian cancer stem cells (CSCs) expressed ROR1. UC-961, a humanized anti-ROR1 monoclonal antibody, could inhibit migration, spheroids formation, immune-deficient mouse engraftment, and CSCs self-renewal[67]. Dr. Cui then presented the latest study to confirm the relationship between leukemia-cell expression of ROR1 and clinical progression[68]. In this study, transcriptome analyses indicated that CLL cases with low-to-negligible ROR1 (designated as $ROR1^{Neg}$) could be distinguished from CLL cases that expressed normal levels of ROR1 (designated as $ROR1^{Pos}$) in an unsupervised gene-expression clustering

analysis. High-level CLL-cell expression of ROR1 was associated with more aggressive disease in 1568 patients followed by clinical investigators in the CLL Research Consortium (CRC). Exogenous *Wnt5a* could enhance the proliferation of $ROR1^{Pos}$ CLL cells induced by CD154 in media supplemented with interleukin (IL)-4 and IL-10, an effect that could be inhibited by UC-961 (cirmtuzumab)[69]. An interaction between ROR1 and ROR2 that is required for WNT5A/GTPase signaling promotes leukemia chemotaxis and proliferation[69]. Cirmtuzumab inhibited engraftment of $ROR1^{+}$ leukemia cells in immune-competent ROR1-transgenic mice and MEC1-ROR1 cells in immune-deficient mice[69]. Bruton's tyrosine kinase (BTK) inhibitor Ibrutinib cannot induce complete responses (CR) or durable remissions without continued therapy. This indicates that alternate pathways may contribute to CLL growth/survival, which are independent of BCR-signaling. Cirmtuzumab could inhibit WNT5A-induced RAC1 activation in CLL treated with ibrutinib. These preclinical observations provide a rationale for combination therapy of cirmtuzumab with BTK inhibitors for patients with CLL or other B-cell malignancies that express ROR1[70]. Taken together, it took more than ten years from discovery of the cancer specific gene ROR1 to the first-in-class monoclonal antibody targeting ROR1 in conducting a phase 1 clinical trial (NCT02222688)[71,72]. Cirmtuzumab might provide new cancer-targeted therapies for patients with cancers such as leukemia, lymphoma and solid tumors.

5. Session on "inflammation & diseases" chaired by Dr. Zhuowei Hu

5.1. Plenary lecture on "inflammation and insulin resistance—galectin 3: new insight into inflammation induced insulin resistance" by Dr. Pingping Li

In obesity, macrophages and other immune cells accumulate in insulin target tissues, leading to a chronic inflammatory state and insulin resistance. Dr. Li's research is focused on the molecular interaction between chronic inflammation and insulin resistance. Dr. Li first gave a brief introduction about current trends of obesity and the multiple consequences of insulin resistance. $CD11c^{+}$ macrophages play a key role in the promotion of a chronic inflammatory state and insulin resistance[73]. Furthermore, Dr. Li explained that transcriptional control by nuclear factors (NRs), including PPARγ and others, contributes to obesity-induced chronic inflammation. Adipocyte-specific nuclear receptor corepressor (NCoR) deletion decreases CDK5-mediated phosphorylation of $PPAR\gamma^{S2\ 73}$, derepresses PPARγ function, and leads to insulin sensitivity and decreased inflammation[74]. Macrophage-specific NCoR deficiency enhances the expression of genes that direct the biosynthesis of palmitoleic acid and $\omega 3$ fatty acids, and inhibits enhancer/promoter histone dimethylation of inflammatory genes[75]. Evidence indicates that obesity associated with insulin resistance leads to increased levels of pro-inflammatory cytokines, such as TNF- and IL-1, which interfere with insulin signaling to induce insulin resistance. However, therapeutic efforts focusing on inhibition of these cytokines to ameliorate inflammation-induced insulin resistance have had limited success in clinical studies. Current treatment options for insulin resistance and type 2 diabetes are not perfect. Many focus on management of blood glucose levels or lifestyle changes, and few targets causal factors that render important metabolic tissues resistant to insulin. Therefore, there is a critical need for new therapies that prevent obesity-associated processes leading to insulin resistance. Dr. Li's previous research found that, after switching the diet of obese mice from a high fat diet (HFD) to normal chow (NC), adipose tissue $CD11c^{+}$ macrophages expressed much lower levels of galectin-3 (Gal3) compared to mice maintained on a HFD[76]. Meanwhile, there was a reduction in inflammation and insulin resistance in these diet-switched mice, despite retaining the same number of adipose tissue $CD11c^{+}$ macrophages. Therefore, Dr. Li hypothesized that Gal3 might promote obesity-induced insulin resistance, providing a link between inflammation and insulin resistance.

Dr. Li then presented a recent study to validate this hypothesis. Dr. Li showed that Gal3 as a lectin mainly secreted by macrophages is elevated in people with obesity, as well as obese mice. Administration of Gal3 to lean mice causes insulin resistance and glucose intolerance, whereas inhibition of Gal3, through either genetic or pharmacologic loss-of-function, improved insulin resistance in obese mice. *In vitro* treatment with Gal3 directly increased macrophage chemotaxis, reduced insulin-stimulated glucose uptake in myocytes and adipocytes, and impaired insulin-mediated suppression of glucose output in primary mouse hepatocytes, indicating that Gal3 induces cellular insulin resistance in all 3 major insulin target cells. Importantly, Gal3 could bind directly to the insulin receptor (IR) and inhibit downstream IR signaling. These observations elucidated a novel role for Gal3 in hepatocyte, adipocyte, and myocyte insulin resistance, suggesting that Gal3 can link inflammation to decreased insulin sensitivity. Inhibition of Gal3 could be a new approach for the treatment of insulin resistance and type 2 diabetes. Dr. Li concluded that their study not only teases out the complex relationship between obesity-related inflammation and insulin resistance, but also identifies a promising drug target[77].

5.2. Short talks on fibrotic diseases by Dr. Xiaowei Zhang and Dr. Xiaoxi Lv

In this section, Dr. Zhang and Dr. Lv presented their latest findings on hepatic fibrosis and pulmonary fibrosis, respectively. In the short talk titled as "targeting the Trib3/p62 interaction ameliorates hepatic fibrosis by restoring the IL17A/STAT3-suppressed autophagy of hepatocytes", Dr. Zhang gave a brief introduction on hepatic fibrosis as the major determinant of morbidity and mortality in patients with liver diseases. Although good progress has been made in the understanding of the pathogenesis of hepatic fibrosis in recent years, the effective antifibrotic agents to prevent or even reverse hepatic fibrosis are an unexplored area for drug development. Dr. Zhang is attempting to define whether hepatocytes directly respond to IL-17A stimulation, which is associated with the development of hepatic fibrosis. In their study, they found that fibrotic liver tissue expressed higher levels of IL-17A, IL-17R and its transcription factor RORγt than control liver tissue. Using the bile duct ligation (BDL)- or thioacetamide (TAA) injection-induced mouse models of hepatic fibrosis, they observed that neutralizing IL-17A promoted the resolution of cholestatic or hepatotoxic liver injury-induced inflammation, attenuated hepatic fibrosis, and increased animal survival. Antagonism of IL-17A inhibited the phosphorylation of signal transducer and activator of transcription 3 (STAT3) and restored autophagy activity in fibrotic liver tissues. Blocking STAT3 by a STAT3 inhibitor STATTIC or by STAT3 siRNA protected from the IL-17A-induced autophagy suppression in hepatocytes. Moreover, the transcription of pseudokinase tribbles 3 (TRIB3), a well-known stress sensor, could be activated by STAT3. The higher expression of TRIB3 was found

in human cirrhosis tissues in comparison with control liver tissues, which correlated positively with the expression of IL-17A and the phosphorylation of STAT3. IL-17A/STAT3-enhanced TRIB3 interacted with autophagic receptor SQSTM1 (p62) and caused p62 accumulation and suppressed autophagy flux. Silencing TRIB3 expression reversed the IL-17A-suppressed autophagy in hepatocytes, which were supported by the *in vivo* findings that interrupting the TRB3/p62 interaction restored autophagy activity in hepatocytes and protected against BDL or TAA-induced hepatic fibrosis. In the end, Dr. Zhang concluded that the IL-17A-STAT3-TRIB3 signaling pathway contributes to the pathogenesis of hepatic fibrosis through suppressing autophagy and the TRIB3/p62 interaction is a potential therapeutic target for the treatment of fibroproliferative liver diseases[78]. Dr. Xiaoxi Lv first gave a background introduction about pulmonary fibrosis (PF), and some common features between PF and lung cancer[79]. Lung epithelial cell injury is commonly considered as an initiating factor for PF. Dr. Hu's laboratory is addressing whether the epithelial-mesenchymal communication of the injured lung epithelial cells play key role in the development of PF and numerous chronic lung diseases. Their current pilot results support the possibility of new therapeutic targets for the development of anti-PF drugs.

6. Summary

A number of talks presented at the 2017 International Workshop of CAMS Initiative for Innovative Medicine on Tumor Immunology have been reviewed with regard to recent important findings on the roles of immunotherapy and inflammation in cancer. These exceptional presentations, subsequent questions, and insightful discussions shall undoubtedly stimulate further studies on the regulatory mechanisms underlying the crosstalk between immune cells and tumor cells, which will ultimately advance the field of chronic inflammatory diseases and cancer treatment.

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