



Annals of Biomedical Research: Some Biomedical Challenges and Perspectives

Nishizawa K*

School of Medical Technology, Teikyo University, Japan

Editorial

This editorial marks the start of the second volume of Annals of Biomedical Research (ABR). Given that many open access journals are born nowadays but only few enjoy the volume two, this situation is something that cannot be taken for granted. On behalf of the editorial board members, I would like to express my gratitude to the authors, whose significant findings and insights helped ABR to gain this momentum.

Although it is too premature to appraise the impact of this journal on biomedical community, it is encouraging that several ABR papers published in Volume 1 show interdisciplinary features. Odanaka and Watanabe [1] extended their previous study on several antigens of *Bordetella pertussis* with potential usefulness for serodiagnostics. This line of study addresses the problem that diagnosis based on detection of *B. pertussis* is often difficult due to an early elimination of the bacteria in the course of the disease. They newly used 2D-polyacrylamide gel electrophoresis (PAGE) followed by immunoblotting for antigen selection, and also addressed the question concerning species specificity of the antigens. Although the sample size was limited, their workflow represents a cost effective approach to enrich such antigens.

Matsuda et al. [2] focused on the patients with Crohn's disease who had shown attenuated response to previous treatments with anti-tumor necrosis factor (TNF) antibodies. Their study showed a potential benefit of the oral medication with budesonide, a glucocorticoid, for such patients. This is a worthwhile finding given that a substantial fraction of patients undergoing anti-TNF treatment show attenuated or inadequate response.

Ogata et al. [3] reported early structural changes of acinar tight junctions in a pancreatic ligation rat model. They observed structural features suggestive of increased paracellular permeability due to leaky tight junction as early as two hours after ligation. This finding adds to recent researches on nociception, the sensory nervous system response to various stimuli including chemical mechanical and thermal stimuli that usually triggers a variety of physiological and behavioral responses. Even in the absence of morphologically clear systemic inflammation, very local proinflammatory factors such as leukotriene B4 and substance P that is released upon activation of transient receptor potential vanilloid 1 (TRPV1) channels are likely to play key roles. Further analyses will focus on detailed dynamics of such molecules that link mechanical stimulation and disruption of tight junction.

We also had a chance to disseminate notable population-based studies. Using a longitudinal cohort based on annual health checkup of Japanese adults, Seki et al. [4] showed that even in the non-obese population with body mass index (BMI) < 25 kg/m², weight gain is a risk factor for higher incidence of diabetes and that reducing or keeping body weight may be beneficial for prevention of diabetes. Non-obese populations in East Asian countries are known to be relatively prone to diabetes compared to Western populations. This study adds new details supporting the notion that, while non-obese Asian populations reduced insulin secretion rather than insulin resistance is often considered the key issue, their findings point to a view that such populations also get benefit from weight control as is the case with obese diabetes in which insulin resistance is the predominant factor. Seki et al. [5] also discussed the data on the association of serum C-reactive protein (CRP) concentration to other metabolic syndrome-related parameters. Of practical merits, several improved conventional CRP assays that measure 1 mg/L CRP with a coefficient of variation (CV) lower than 10% with low cost appeared to be suitable for population-based study on CRP as well as assessment of the risk for cardiovascular disease. The authors also discussed the current challenges in the standardization to reduce between-manufacturer and between-institution differences both in high-sensitive CRP (hs-CRP) assays and in conventional CRP assays, which compromise the merits of hs-CRP measurement.

Our molecular dynamics simulations showed that lipid-raft forming lipids (i.e., cholesterol and phospholipids harboring saturated fatty acids) can stabilize the dimeric state of transmembrane peptides in a sequence-nonspecific fashion [6]. It is likely that regardless of the amino acid sequence, hydrophobic helical transmembrane peptides show high propensity for dimerization/multimerization in the lipid-raft like bilayer relative to non-raft-like bilayers. However, experimental data that serve as references to such with computational data are limited. It is hoped that the dimerization energy is measured for many more peptides in *in vitro* systems.

As a whole, these papers highlight the usefulness of diverse approaches can be useful to discussed biomedical problems utilizing diverse approaches. These contributions prompt me to ponder over the unique value or niche of biomedicine. Compared to more specialized journals, biomedical journals may be suitable to the areas that are associated with complex pathophysiology requiring multidisciplinary studies.

I personally had a chance to be involved in a research project concerning the role for innate immunity in an experimental model of septic shock. Severe insults or inflammation causing an organ damage, such as acute liver failure, often leads to multiple organ dysfunction and systemic immune paresis that result in sepsis [7]. Even in the cases with major trauma, hemorrhagic shock, anesthesia and surgery, blood transfusion, and drug-induced organ injury, the immunosuppressive state can occur after initial phase of sterile inflammatory response. The immunosuppressive state increases the risk of sepsis. Sepsis and septic shock themselves are also the causative factors for organ dysfunction.

Here I would like to draw attention to the controversy concerning the criteria of sepsis [8]. The diagnostic criteria released by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine in 2016 has eliminated systemic inflammatory response syndrome (SIRS) from the criteria and increased the relative weight on sequential organ failure assessment (SOFA) for the diagnosis. Dr. Simpson considers that SIRS is an important harbinger of life-threatening organ dysfunction, and that abandoning the use of SIRS in sepsis definition and focusing on findings more highly predictive of death could encourage waiting, rather than early and effective intervention. As the aforementioned insults often precede sepsis development, sepsis has variable clinical presentations. Such diversity may make extracting common features among cases difficult, possibly motivating the committees to rely on the relatively advanced stages of sepsis for clear definition. Although it is beyond my scope to discuss this controversy further, it urges our deeper understanding of pathophysiology and, in particular, commonalities and distinctive patterns in diverse types of sepsis/septic shock.

From biomedical perspectives, sepsis/septic shock is an area in which animal model experiments have made a significant contribution. Such a contribution helped our understanding of the role of endotoxin tolerance, for example. In recent analyses of immune tolerance, not only macrophages but also dendritic cells and neutrophils have become the focus. Intensive research focusing on neutrophils and neutrophil extracellular traps (NETs) formation activity and its relationship with thrombosis and organ failure in sepsis/septic shock is underway. Despite these efforts, there remain many questions significant for clinical improvement. A part of clinical challenge arises from the feature that the immunosuppressed state cannot be generalized and some functions remain normal. As such, immune paresis toward certain types of bacteria becomes more severe than others. Further clinical challenges may arise from the fact that, rather than simple transition from initial proinflammatory to anti-inflammatory states, these functionally opposing processes occur simultaneously, and such simultaneous processes need to be dissected at higher spatial and temporal resolution. Adding another layer of complexity is the interpretation that septic shock causes not only immune dysfunction but also pathological accumulation of reactive oxygen species (ROS) and the depletion of glutathione, a master antioxidant of the cell [9]. However, it is poorly understood how such an excess

of ROS production associates with different states of inflammation and immune response. So, much remains unknown. Studies to find reliable biomarkers for the immunosuppression state and pro-resolving state are warranted.

Although such challenges remind us of our long way toward improved treatments in many clinical forefronts, I think we generally have a bright prospect for scientific achievements that can benefit clinical medicine in the coming decade. I might add that one of the pleasures of editing articles with wide implications to both clinical and basic medicine is renewing my recognition that the combination of clinical researches and biological models drives medical science. Hopefully, the word, biomedicine, may encourage researches focusing on any diseases to become a starting point to build a bridge between clinical and basic medicine.

As I stated in the inaugural editorial, we are committed to the rigorous peer-review of all submitted manuscripts. Nonetheless, one of important merits of open access journals like ours is rapid dissemination of insightful, bold and constructive discussions. We also think that, with careful descriptions of conditions and limitations of analyses, rather preliminary datasets still have a chance for dissemination in various formats. So, I hope we can receive submissions in diverse formats including discussion based on relatively preliminary data, unpublished materials, and commentaries/mini-reviews on any biomedical topics. Thanks to the information-technology revolution over the last decades, we now take for granted instant access to published data anywhere on this planet, making it much easier to conduct, for example, a metaanalysis that was hampered not that long ago. Our honest goal is to help budding researchers who seek a journal with a low publication fee without compromising the quality of reviewing/editing.

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***Corresponding author:** Kazuhisa Nishizawa, MD PhD, School of Medical Technology, Teikyo University, Itabashi, Tokyo, Japan; kazunet@med.teikyo-u.ac.jp

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