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EDITORIAL

JECM: TMU Proteomics Genomics Transcriptomics

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1. *JECM* Visibility and Significance

In the process of becoming acquainted with the challenge of starting a new journal, we all recognize the need for more rapid and timely submissions that of course are peer reviewed, and therein lies the first challenge—that of finding dependable and expert referees. Because the *Journal of Experimental and Clinical Medicine* (*JECM*) is just beginning, clearly there may be the difficulty of forging a unique path, a trajectory that thrusts *JECM* at least nearly avant garde not only for the Asia Pacific region but internationally as well. We have prestigious backing, i.e., Taipei Medical University (TMU), and an equally well-known publisher Elsevier. Now we must decide on the mission. What will make *JECM* unique when it is planted onto soil that is already flourishing and growing? Perhaps the uniqueness now is solid support as print copy and enthusiasm of the TMU President who founded *JECM*.[1] Then he established a fully endorsing Editorial Board. Second, *JECM* has the potential to thrive with a unique mission, through my own successful efforts at creating two other journals: *Developmental and Comparative Immunology* and *eCAM*, both published by Elsevier.

It is not the intent of *JECM* to overlap or engage in conflict with these two since the goals are different despite my own views of experimental and clinical medicine being firmly rooted in a background influenced by my own contributions as a biologist.[2] No one will dispute the origins of biomedical research as an offshoot of basic biological sciences—the thrust and trajectory are different. *JECM*, like all other biomedical journals, owes its existence to biology.[3] We wish to consider papers from outside the Asia-Pacific region and those outside Taiwan. Some within the walls of Taiwan may not know about *JECM*—even some at TMU may not be so intimately aware of this prescient initiative. So editorials, at least for this one issue of volume two, will focus on cutting edge research done at TMU and in Taiwan. We need to inform our home base and nearby relations that *JECM* exists. Admittedly, the publishing world is small; still, the day-to-day activity of academicians often obscures what is really in our own backyard! For this reason, I present a rapid look at papers from TMU.

To begin, I focus on proteomics, genomics, and transcriptomics. Invariably, the definitions and the examples may overlap. Why choose these to write about? In my opinion, they represent cutting edge technology designed to bring relevant findings of biomedical research closer to a more finite understanding of and application to medicine within the current limits of knowledge. And in so doing, our findings are clearly more unified and relevant—not obscure—but transparent. Those that are briefly reviewed are the works from various research groups at TMU and not others in Taiwan. Clearly, from the totals in excess of 12 cited in PubMed, there are only a few from TMU with most derived from other Taiwanese biomedical groups. The results suggest that for the three arbitrary parameters, there may be a need to increase these approaches.

2. Proteomics

Proteomics analyze the full set of proteins in a cell type or tissue and the changes during various conditions,

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and are the large-scale study of proteins, particularly their structures and functions. Proteins are vital parts of living organisms, as they are the main components of the physiological metabolic pathways of cells. The term "proteomics" was first coined in 1997 to make an analogy with genomics, the study of genes. The word "proteome" is a blend of "protein" and "genome". The proteome is the entire complement of proteins, including modifications made to a particular set of proteins, produced by an organism or system. From the Graduate Institute of Clinical Medicine, College of Medicine, Chen and colleagues[4] analyzed acute hypoxia and found that it enhances proteins' S-nitrosylation in endothelial cells. Hypoxia-induced responses are frequently encountered during cardiovascular injuries. Hypoxia triggers intracellular reactive oxygen species/nitric oxide (NO) imbalance. The S-nitrosylated cysteine residue on tropomyosin (Cys 170) and beta-actin (Cys 285) was further verified with the trypsic peptides analyzed by MASCOT search program. Further understanding of the functional relevance of these S-nitrosylated proteins may provide a molecular basis for treating ischemia-induced vascular disorders.

In another study from the Department of Dermatology, TMU Hospital, Lee and colleagues[5] investigated transdermal delivery of peptides and related vaccines due to implications for treating and preventing diseases. However, this delivery method is limited due to low permeability of the stratum corneum. These investigators sought to enhance and control skin permeation of peptides and related vaccines using an erbium:yttrium-aluminum-garnet (Er:YAG) laser. They employed the nude mouse, a unique animal model. Amounts of peptide transported through nude mouse skin were measured using a Franz diffusion apparatus. The result of confocal laser scanning microscopy indicated a significant increase in the skin deposition of peptides into laser-treated skin. In an *in vivo* study, mouse skin was treated with the laser followed by skin vaccination with a lysozyme antigen. Results revealed for the first time that laser treatment with no adjuvant or penetration enhancer significantly enhanced the production of serum antibodies by three-fold. To reveal the mechanisms underlying these changes, a proteomic technique combined with mass spectrometry was used, an apparent first report of using a laser to immunize intact animals.

3. Genomics

Genomics analyzes the genomes of organisms aimed at determining the entire DNA sequence thus revealing fine-scale genetic mapping. There are efforts to reveal intragenomic phenomena such as heterosis, epistasis and pleiotropy. Genomics owes its origins to the first sequence of a virus and a mitochondrion. Understanding the full genomes has given rise to functional genomics including patterns of gene expression. The most important tools are microarrays and bioinformatics. Only one report appeared in the category of genomics and two overlapped with a cross listing with proteomics. This also was derived from a group in the Department of Biochemistry, School of Medicine, TMU. The work investigated one of the most debilitating of nervous system disorders. Huang and colleagues[6] analyzed amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disorder disease. Ten percent of ALS patients are congenital (familial ALS), and the other 90% are sporadic (SALS). Mutations found in the Cu,Zn-SOD cause 20% of familial ALS due to its low enzyme activity. This group hypothesized that heavy metals may interfere with the structure of Cu,Zn-SOD protein to suppress its activity in certain SALS. They expressed and characterized the recombinant human Cu,Zn-SOD under various concentrations of Cu^{2+}, Zn^{2+}, and Cd^{2+}. By atomic absorption spectrophotometry, they found that adding cadmium significantly increased cadmium ion content, but reduced its Zn^{2+} content and enzyme activity of the Cu,Zn-SOD protein. Circular dichroism spectra revealed that the secondary structure of Cu,Zn-SOD/Cd is different from Cu,Zn-SOD, but close to apo-SOD. Moreover, the effect of cadmium on Cu,Zn-SOD is to induce neural cell apoptosis. To further investigate the mechanism of neural cell apoptosis induced by cadmium, they then used proteomics to analyze the altered protein expressions in neural cells treated with cadmium. The altered proteins included cellular structural proteins, stress-related and chaperone proteins, proteins involved in reactive oxygen species, enzyme proteins, and proteins that mediated cell death and survival signaling. Taken together, they demonstrated that cadmium decreased the content of Zn^{2+} and changed the conformation of Cu,Zn-SOD protein, causing a decrease in its enzyme activity and oxidative stress-induced neural cell apoptosis.

4. Transcriptomics

Transcriptomics is the branch of chemistry that deals with the messenger RNA molecules produced in an individual or population of a particular cell type. Now here are the search results from several research units at TMU. A transcriptome constitutes the set of all RNA molecules, including mRNA, rRNA, tRNA and non-coding RNA produced in one or a population of cells. Or the term can be applied to the total set of transcripts in a given organism or to the specific subset of transcripts found in a particular cell type. Unlike the genome, that is more or less fixed for a given cell line (excluding mutations), the transcriptome can vary with external environmental conditions. From the Department of Emergency and Critical Care Medicine, Tsai et al[7] investigated

the mechanism underlying how transforming growth factor-β (TGF-β) represses interleukin-1β (IL-1β)-induced proteinase-activated receptor-2 (PAR-2) expression in human primary synovial cells (hPSCs). TGF-β induced connective tissue growth factor (CTGF), which in turn repressed PAR-2 expression by inhibiting IL-1β-induced phospho-p38 level. TGF-β prevented osteoarthritis from progression with the anabolic ability to induce CTGF production to maintain extracellular matrix integrity and to downregulate PAR-2 expression, and the anti-catabolic ability to induce tissue inhibitors of metalloproteinase-3 production to inhibit matrix metalloproteinases (MMPs) leading to avoidance of PAR-2 overexpression. Because IL-1β-induced PAR-2 expressed in hPSCs might play a significantly important role in the early phase of osteoarthritis, PAR-2 repression by exogenous TGF-β or other agents might be an ideal therapeutic target to prevent the progression of osteoarthritis.

Another paper comes from the Graduate Institute of Medical Sciences by Chang and colleagues.[8] ATP activates the mitogen-activated protein kinase (MAPK) signaling pathway in various systems. However, there is sparse information on signaling events and the effects in human endometrial stromal cells. This study demonstrated the expression of the P(2U)/P2Y(2) receptor in human endometrial stromal cells by reverse transcription-PCR (RT-PCR). The effects of ATP on the expression of MMP genes were confirmed by semiquantitative RT-PCR. Apparently, this reveals for the first time that ATP-induced nuclear translocation of phospho-ERK1/2 mediates MMP gene expression in human endometrial cells. For application, these results support the view that the ERK1/2 signaling pathway is involved in mediating ATP actions in the human reproductive system.

Lee and colleagues[9] organized a study from the Graduate Institute of Biomedical Informatics, that proposed the Epstein-Barr virus (EBV) as closely associated with nasopharyngeal carcinoma (NPC). However, the molecular mechanisms involved in the effect of EBV on NPC host genes must be defined. Statistical analysis revealed that EBV seems to prefer targeting more genes from the differentially expressed group in NPC cells than those from the ubiquitously expressed group. This trend is also reflected in log ratios where the EBV-targeted genes of the differentially expressed group origin showed greater log ratios than genes with an origin from the ubiquitously expressed NPC group. When interpreted together, the genome-wide comparative scanning of EBV and NPC transcriptomes successfully revealed that EBV infection exerts an intensifying effect on signals involved in NPC gene expression in breadth (the majority of genes) and in depth (greater log ratios).

From the Department of Obstetrics and Gynecology, Au and colleagues[10] sought to evaluate the transcription and translation ability of mitochondria in terminally differentiated granulosa cells that were incubated with ionic calcium. Results revealed dose-dependent increases in RNA expressions of the four genes analyzed from granulosa cells cultured in a serial concentration of calcium ions. This effect was abolished when cells were preincubated with the extracellular calcium-chelating agent, ethylene glycol-bis (2-aminoethylether)-N,N,N′,N′-tetraacetic acid (EGTA). The effect of ionic calcium on both the nuclear- and mitochondrial-encoded subunits was also determined. Expression levels of mitochondrial transcription factor A in RNA significantly increased in granulosa cells that had been exposed for 24 and 48 hours to 0.5 and 1 μM A23187. This is the first report revealing that calcium-dependent increases in transcription and translation levels of both nuclear-encoded and mitochondrial-encoded mitochondrial respiratory enzyme subunits occur, and also indicates that mitochondrial transcription factor A is involved in mitochondrial biogenesis.

Also from the Department of Obstetrics and Gynecology, another study has emerged from the laboratory of Tai et al.[11] When many types of cell surface receptors are activated, MAPKs are activated. This group demonstrated earlier an effect of extracellular ATP on ERKs and gonadotropin-induced progesterone secretion. This suggests the significance of ATP in regulating ovarian function. However, much is to be learned about the specific role of ATP in the subsequent MAPK-induced signaling cascade in human granulosa-luteal cells (hGLCs). They designed the present investigation to examine the effect of ATP on activation of the MAPK signaling pathway, including nuclear translocation and the expression of the immediate early genes in hGLCs. Western blot analysis using a monoclonal antibody, which detected the total and phosphorylated forms of ERK1 and ERK2 [p42(mapk) and p44(mapk)], demonstrated that exogenous ATP evoked ERKs in a dose- and time-dependent manner. In contrast, p38 and JNK were not significantly activated after ATP treatment. To examine the translocation of activated ERKs, fluorescein isothiocyanate-conjugated secondary antibody was used to detect the distribution of total and phosphorylated ERKs. Immunofluorescent staining revealed that phosphorylated ERKs were translocated from cytoplasm into nucleus subsequent to 10 μm of ATP treatment. To analyze the gene(s) induced by exogenous ATP, mRNA was extracted from hGLCs in the presence or absence of 10 μm of ATP. Gene array for 23 genes associated with members of the mitogenic pathway cascade and immediate early genes revealed that the expression of early growth response 1 and c-raf-1 was increased. This most probably represents the first demonstration of the ATP-induced nuclear translocation of MAPKs in the human ovary. These results suggest that the MAPK signaling pathway plays a role in mediating ATP actions in the human ovary.

5. Perspectives

The future seems bright and promising for *JECM* given the universal enthusiasm at all levels involved. We must accomplish great feats despite stiff competition because of the existence of a wide array of similar journals. We wait to attract the best papers and of course maintain the highest standards of evidence-based papers that have been subjected to rigorous peer review.

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