

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

Biomedical Journal

journal homepage: [www.elsevier.com/locate/bj](http://www.elsevier.com/locate/bj)

## Editorial Note

# An area of greatest vulnerability - Recent advances in kidney injury

Aila Akosua Kattner\*

Berlin, Germany

### ARTICLE INFO

#### Article history:

Received 20 July 2022

Accepted 23 July 2022

Available online 6 August 2022

#### Keywords:

Acute kidney injury

Chronic kidney disease

COVID-19

Surfactant

Metabolomics

Cerebral palsy

### ABSTRACT

In this issue of the *Biomedical Journal* the reader is provided with an insight into the latest observations and advances in acute kidney injury as well as chronic kidney disease. The current SARS-CoV-2 variants are reviewed, and the role of long non-coding RNA in HIV therapy is explored. Furthermore, the potential of metabolomics as means to diagnose multiple sclerosis as well as tuberculosis is presented. Other topics of this issue include the restoration of the spermatogonial stem cell niche; atherosclerosis and the use of improved ultrasound images; and the effect of transcranial magnetic stimulation in patients with autism spectrum disorder. Finally, it is shown how continuous passive motion can be used as supportive therapeutic approach in children with cerebral palsy, and minimally invasive surgery is presented as valid alternative in cases of spine metastasis.

## Spotlight

According to ancient Greek and Byzantine texts the kidneys had a special meaning and function for the according societies. They were used in the context of the cultural heritage and for centuries kidneys would serve priests, doctors and lay persons as sacrificial offers, source for medicaments or plain food [1]. In the Old Testament the kidneys are mostly mentioned as part of sacrificial animals. Only the best of everything was supposed to be offered, hence special instructions were given on how animal kidneys were to be presented on the altar. The significance of the kidneys within this cultural background is underlined by the fact that they are mentioned quite frequently in the Bible: 11 times alone in

terms of sacrificial practices, whereas reference to the heart as anatomic organ is made rarely, and only one reference to the liver is made [2].

While Syrians and Arabs considered the liver as center of life, the kidneys held a place of more importance in Israel. The kidneys were considered as seat of conscience, emotions, desire, and wisdom as well as seat of secret thoughts. They were seen as area of greatest vulnerability [2,3].

Insights into the causes of renal disease was advanced beginning 4000 years ago thanks to taking up the practice of written records of observations and thoughts. Some of the first medical giants leading the way to the clinical nephrology of the 21st century include the ancient Egyptians, the Ancient and Byzantine Greeks, Persian Physicians as well as a few Renaissance Physicians [4]. In the East medical education

\* Corresponding author. Freelance Journalist, Berlin, Germany.

E-mail address: [aila.kattner@gmail.com](mailto:aila.kattner@gmail.com).

Peer review under responsibility of Chang Gung University.

<https://doi.org/10.1016/j.bj.2022.07.006>

2319-4170/© 2022 Chang Gung University. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

were originally not to as institutionalized in ancient times as it was the case in the West. Preparation for a medical career often occurred through self-learning or following a family member into the profession. Providing written teachings in an accessible language was key to opening the access to studying medicine [5].

Almeida et al. examined the role of bone-marrow-derived mesenchymal stem cells (MSC) in the remodeling of fibrotic kidney parenchyma [6]. Renal fibrosis is the common, final outcome of most progressive chronic kidney diseases (CKD). It also serves as a reliable determinant of renal insufficiency. Renal fibrogenesis is a dynamic process involving almost all types of cells in the kidney and complex inflammation cascades [7]. MSC are adult stem cells with the ability of self-renew, that also exhibit multilineage differentiation. The ease of harvest, the quantity obtained and the availability from various sources make MSCs good candidates for experimental or clinical applications [8].

Almeida et al. showed in a CKD animal model that anti-fibrotic and anti-inflammatory events were orchestrated through transplanted MSCs, reversing renal fibrosis and promoting renal morphological restoration [6].

Although traditionally considered as separate diseases with differing etiologies, CKD and acute kidney injury (AKI) have shown to be linked and seem to even promote one another. CKD is recognized as a risk factor for the development of new AKI, and AKI may lead to de novo or accelerated CKD. Both are characterized by a decreased glomerular filtration rate and increased proteinuria [9,10].

In this issue of the *Biomedical Journal*, Chang et al. provide us with an insight into the relationship between long non-coding RNA (lncRNA) *Opa* interacting protein 5-antisense RNA 1 (*OIP5-AS1*) and the progress of AKI [11].

lncRNAs account for 80% of ncRNA. They do not possess protein coding function, and participate in regulation at epigenetic, transcriptional, post-transcriptional, translational, and post-translational levels. lncRNAs usually function in complex interaction with genes and proteins, and depending on their specific subcellular localization and function, they can affect gene expression on multiple levels. lncRNAs are consequently involved in genomic imprinting, chromatin modification and remodeling, alternative splicing, cell differentiation and cell cycle regulation. lncRNAs are also playing a part in many diseases [12,13].

lncRNA *OIP5-AS1* is highly expressed in the nervous system, and has been evaluated mostly for its role in malignant conditions such as neoplastic transformation. *OIP5-AS1* influences carcinogenesis in different ways. It acts as a sponge for various microRNAs (miRNAs), thus partaking in cancer initiation and progression. Furthermore, *OIP5-AS1* expression is linked to epithelial–mesenchymal transition (EMT), a process that facilitates metastasis. *OIP5-AS1* also upregulates the expression of the oncogenic transcript *OIP5*, and can thus exert an effect on the activity of various signaling cascades [14].

miRNAs are ncRNA molecules with pivotal role for fine-tuning RNA expression. In cancer cells, abnormal expression of miRNAs can lead to cancer development. miR-144-5p is one miRNA whose aberrant expression is involved in tumorigenesis [11,15–17] [see Fig. 1].

Chang et al. explored to role of *OIP5-AS1* in the progression of AKI in mice and *in vitro*. The team predicted potential targets of miR-144-5p and successfully identified *OIP5-AS1* as sponge for miR-144-5p. Additionally, pyruvate kinase M2 (*PKM2*) was also found to be a direct target of miR-144-5p. *OIP5-AS1* was significantly downregulated in AKI mice and

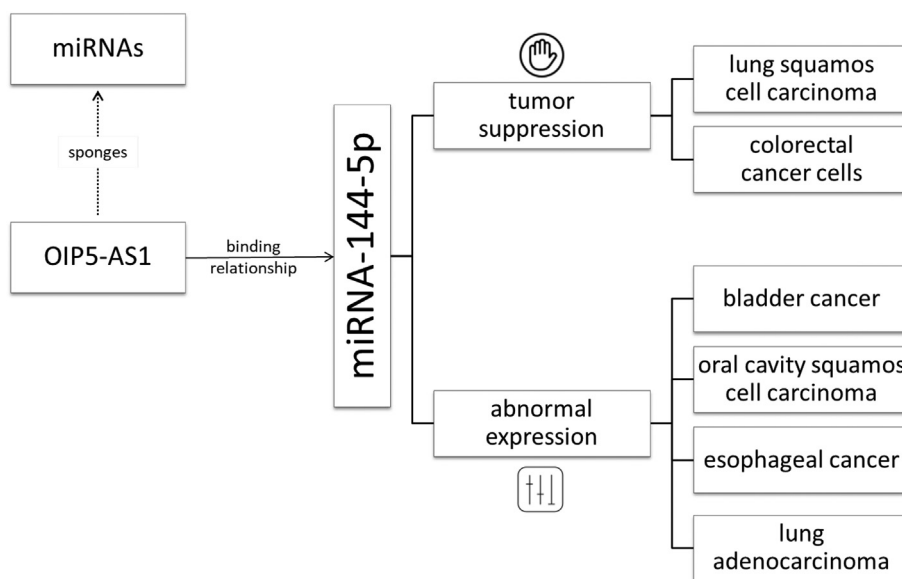


Fig. 1 The involvement of miRNA-144-5p in human cancer. miRNA-144-5p has a binding relationship to the lncRNA *OIP5-AS1* that is known for sponging miRNAs (competing endogenous RNA). miRNA-144-5p may exert an inhibition in some human cancers whereas its abnormal expression is observed in other series of human cancers.

its overexpression promoted cell growth while reducing apoptosis in human renal tubular HK-2 cells [11].

## Also in this issue

### Reviews

#### *Ignorance isn't strength*<sup>1</sup>

Since 2019 the disease caused by SARS-CoV-2 challenges individuals and institutions such as public health systems on a global level. The emergence of COVID-19 variants of concern (VOC) contributes to the complexity of the situation as those variants may spread more easily, cause a more severe disease pattern, escape the body's immune response, change clinical presentation or decrease effectiveness of known tools.<sup>2</sup>

The evolution of SARS-CoV-2 is internationally closely monitored, *inter alia* to adapt global strategies to reduce transmission and avoid introduction into animal populations. VOCs are also an economical stressor, considering that economic growth experienced a rebound in 2021, but will slow down over the next two years due to new threats from COVID-19 variants according to the UN. Especially fragile and conflict-affected economies will be vulnerable to this setback, vaccine equity is another paramount factor in this context.<sup>3</sup>

In their review, Chen et al. summarize the current knowledge of epidemiological and clinical variant features, and discuss possible vaccine response strategies to reduce the burden of COVID-19 [18].

#### *Targeting the latent reservoir in HIV*

HIV disease can be managed through a combination of anti-retroviral drugs. The current antiretroviral therapy (ART) does not cure HIV infection, however, it highly suppresses viral replication within an individual's body. This allows the immune system to strengthen, and fight off opportunistic infections and some cancers. Since 2016 WHO has recommended that all people living with HIV should be provided with lifelong ART. By 2021, 187 countries had committed to this guideline, covering 99% of all people living with HIV globally.<sup>4</sup>

A major barrier for current ART to provide a cure from HIV infection lies in the latent cellular reservoir of HIV. Individual lncRNAs are involved in regulation of HIV expression. Thanks to their tissue and cell-type specificity, they may hence present targets of choice for HIV latency reversal [19].

<sup>1</sup> The title refers to the dystopian science fiction novel "1984" by Orwell, where citizens are blasted on a daily basis with the slogan "War is peace, freedom is slavery, ignorance is strength." by their government. Source: <https://study.com/learn/lesson/war-is-peace-1984.html>, last access 7/18/2022.

<sup>2</sup> <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-%28covid-19%29-variants-of-sars-cov-2>, last access 7/18/2022.

<sup>3</sup> <https://news.un.org/en/story/2022/01/1109582>, last access 7/18/2022.

<sup>4</sup> <https://www.who.int/news-room/fact-sheets/detail/hiv-aids>, last access 7/9/2022.

Liu et al. present a review of the role of lncRNAs in HIV-1 transcription regulation, summarizing the latest research progress and potential application in HIV-1 therapy [20].

#### *Investigating the tiny parts in multiple sclerosis*

The emerging field of metabolomics offers an insight into the tissue specific changes as well as temporal dynamics of metabolite levels in response to complex disease and monogenic disorders. The method paves the way to precision medicine, however, the analysis remains challenging since the molecules measured have disparate physical properties [21].

Multiple sclerosis (MS) is hypothesized to be an autoimmune disease. Symptoms can range from relatively benign to devastating impacts on the central nervous system, leading to a disrupted communication between the brain and other parts of the body. There is currently no cure for MS, and diagnosis may be delayed due to uncertain symptoms.<sup>5</sup> MS has the highest incident in regions away from the equator [22], is more prevalent in women than in men [23], and may be misdiagnosed for years in up to 50% of patients [24].

Liu, Waters and Rui provide an overview of the applications of metabolomics for investigation of pathways in MS. A number of potential biomarkers, that are available, may advance understanding of MS pathogenesis, improve MS diagnosis and reveal the path for personalizing treatments [25].

#### *To recover a niche*

Stem cells take part in dynamic physiological systems, and their state of either dormancy, self-renewal, or further differentiation is influenced by extrinsic signals. These stimuli include cell-to-cell and cell–matrix interactions and take place in a specific environment, the stem cell niche [26].

Unlike in other niches, spermatogonial stem cell (SSC) niche cells are less capable of adopting a new fate. Hence, in order to restore spermatogenesis, a complete restoration of the stem cell niche is required. Sagaradze et al. review the approach of using multipotent mesenchymal stromal cells (MSCs) to restore the SSC niche. They see a need to developing specific animal models to reveal the role of MSCs as a therapeutic, regenerative approach for idiopathic male infertility through stem cell niche recovery [27].

#### *Surfactant of the future*

Pulmonary surfactant replacement therapy (SRT) is essential in managing respiratory distress syndrome (RDS) in neonates, as it drastically improves survival while reducing respiratory morbidities. However, although the benefits are proven, a number of questions remains to be elucidated, such as if SRT should be used prophylactically at birth for infants at risk for RDS, or selectively to infants with established RDS [28].

Another urgent matter consists in tailoring surfactant therapies to specific respiratory pathologies, which requires for instance determining the composition and structure for

<sup>5</sup> <https://www.ninds.nih.gov/health-information/disorders/multiple-sclerosis>, last access 7/18/22.

various surfactant activity needs. In his review, Pérez-Gil summarizes the principles behind the development of efficient natural, recombinant or synthetic therapeutic surfactants, and furthermore provides an insight into currently promising lines of surfactant research. Mass production of humanized surfactant protein however poses a major bottleneck in the development of next generation therapeutic surfactants [29].

### Original articles

#### *The king's evil*

Tuberculosis (TB) has been accompanying humans since the Paleolithic period. It is hypothesized that the microbe was one essential driver for humans to start settling down around 43,000 years ago to ensure species survival by increasing fertility. Through farming and therefore expanding food production, women were able to balance out infant mortality rates of 50% including the ravages TB would exert on the small hunter-gatherer tribes. Additionally, increasing resistance in females to the *Mycobacterium tuberculosis* complex contributed to the battle against TB.<sup>6</sup>

A form of extrapulmonary TB used to be known as “king's evil” until the 18th century in Europe, as it was believed that the royal touch would cure the disease [30].

TB is a significant cause of death in several developing countries. Additional barriers consist in the lack of specificity and sensitivity of current tools as well as the extensive time needed to quickly obtaining conclusive diagnostic results. Conde et al. therefore made an effort to discover biomarker signatures für TB diagnosis using a Nuclear Magnetic Resonance based metabolomics approach. The team found six promising metabolites that are consistent with the WHO recommendations for a triage test to exclude active TB [31].

#### *I rot – sepsis in acute kidney injury*

Sepsis, the life-threatening, dysregulated immune response to an infective insult, has been first documented in Homer's poems 2700 years ago [32]. 2022 marks the 204th birthday of Ignaz Semmelweis, the pioneer of improved infection prevention and control practices. While working in obstetrics, Semmelweis observed a far lower number of the frequently lethal childbed fever in the ward exclusively staffed with midwives versus the ward staffed with medical students and doctors. Semmelweis hypothesized that the elevated mortality was related to the contamination of the hands of medical students and doctors from autopsies. He recommended measures such as hand washing before moving to the delivery room. This intervention proved effective but made Semmelweis unpopular among students and colleagues. Consequently, he lost his job at the hospital twice and was finally committed to a mental asylum at the age of 47, where he died shortly after admission [33].

Lin et al. performed a retrospective study to predict hospital mortality in patients with sepsis-associated acute kidney injury (AKI). The team performed a dynamic monitoring of AKI from day 1 to day 3 after ICU admission. They concluded

that a deterioration of AKI within this time frame may be a sepsis phenotype predictive of hospital mortality [34].

#### *State-of-the-art object detection*

According to the International Air Transport Association (IATA) the total demand for air travel drastically increased in spring 2022. The number of kilometers travelled by paying customer (Revenue Passenger Kilometers, RPK) for instance rose by 332% in April 2022 versus April 2021. The RPK of some routes is already above pre-pandemic levels. Probable reasons are the lifting of border restrictions and a surge in bookings after two years of lost travel opportunities.<sup>7</sup> Addressing airport traffic jams is one of the challenges that comes with increased travel demands. The use of the machine learning model Mask Region-Based Convolutional Neural Network (Mask R-CNN) is proposed as a fast, low-cost solution for object detection in an image, like for instance detecting airplanes in aerial images provided by drones.<sup>8,9</sup>

Yang et al. combined Mask R-CNN with an additional classification step to detect and identify glomerular lesions. Pathological examination of kidney biopsy requires several, time-intense steps. The team's first-of-its-kind study demonstrated how multiple tasks involved in kidney biopsy interpretation can be captured and simulated by machine learning models. Thus the workload pathologists face might be effectively reduced. Further improvement of the approach potentially allows incorporation of additional input from immunofluorescence and electron microscopy [35].

#### *Young at heart*

In 2017 an observational study was presented that aimed at better understanding the association between pre-industrial lifestyle and low prevalence of coronary artery disease risk factors. The research team assessed coronary atherosclerosis of the Tsimane, an indigenous forager-horticulturalist tribe of the Bolivian Amazon. The Tsimane proved to have the lowest prevalence of coronary atherosclerosis of any population studied. The researchers suggested that despite high infectious inflammatory burden, the protection from vascular aging found in the tribe might be due to their active lifestyle, and a diet mainly consisting of non-processed carbohydrates high in fiber [36]. Thus an 80-year old Tsimane had the same vascular age as an U.S. American in his or her mid-fifties. Most Tsimane never develop any coronary atherosclerosis, suggesting that the disease could be entirely avoided by keeping low LDL cholesterol, low blood pressure and low blood sugar in addition to being physically active and not smoking.<sup>10</sup>

Measuring carotid intima-media thickness (IMT) is an essential indicator of atherosclerosis disease. Naik and team performed a study to investigate the effects of despeckle filters on the automated segmentation of carotid IMT ultrasound images. The team found that while the noise reduction

<sup>7</sup> <https://www.iata.org/en/pressroom/2022-releases/2022-06-09-01/>, last access 7/8/2022.

<sup>8</sup> <https://deepai.org/publication/airplane-detection-based-on-mask-region-convolution-neural-network>, last access 7/8/2022.

<sup>9</sup> <https://viso.ai/deep-learning/mask-r-cnn/>, last access 7/8/2022.

<sup>10</sup> <https://www.sciencedaily.com/releases/2017/03/170317132004.htm>, last access 7/8/2022.

<sup>6</sup> <https://www.germanstrias.org/news/180/tb-has-shaped-human-society-since-the-stone-age>, last access 7/10/22.

filters are not posing a serious additional computational burden, they improve segmentation accuracy [37].

#### On influencing the brain

In the 1950s the Church of Scientology has been founded, promoting a number of beliefs and self-help practices established by its founder.<sup>11</sup> A main concept of the organization's credo is the thetan, an immortal entity considered as the self or human soul that is currently trapped on Earth in a physical body. The thetan is derived from theta, which according to Scientology represents the source of life, and scientologists believe that the Church's setoff techniques free the thetan.<sup>12</sup> Scientology recently raised attention to their cause through an advertisement at the Super Bowl, one of the biggest U.S. sports event, delivering the message to the viewers that they were tied down giants meant to rise at any moment.<sup>13</sup> The Church of Scientology is highly organized, thought to be operating in around 150 countries worldwide with its legal status locally oscillating between a religious organization, a cult or a business [38].

Theta burst stimulation (TBS) is a form of repetitive transcranial magnetic stimulation (rTMS). rTMS is an indirect, non-invasive method generating a magnetic field passing through the scalp. TMS is used as a diagnostic as well as potential therapeutic tool for neurological and psychiatric diseases. rTMS is hypothesized to induce plasticity [39].

Ni et al. performed a small pilot study to better understand the impact intermittent TBS has on adult patients with autism spectrum disorder. The team found *inter alia* therapeutic potential of a 5-day session on clinical symptoms but not executive function [40].

#### Cerebral palsy and a motorized motion device

Muscle tone regulation supports maintaining a normal posture and facilitates movement. As a muscle stretches, the muscle tone may be automatically altered. In the case of spasticity, an increased stretch reflex results in excessive and inappropriate muscle activation. Spasticity is one important neural contributor to muscle hypertonia in children with cerebral palsy (CP) [41].

Originally, the continuous passive motion (CPM) device was developed by Salter. He hypothesized in the 1960s that degenerative changes in cartilage after prolonged immobilization could be improved by continuous movement as opposed to intermittent motion.<sup>14</sup> The joint regeneration progress is facilitated by the movement of synovial fluid allowing improved diffusion of nutrients into the cartilage and removal of waste products [42].

Chuang et al. evaluated soleus hypertonia in individuals with spastic CP after ankle CPM. The research team found that ankle CPM is an effective intervention for the chosen patient

group, and could potentially be employed before gait training to improve ankle joint performance in cases of moderate or severe ankle spasticity [43].

#### Minimal invasive screwing in spine metastasis

Up to 70% of patients with cancer develop spine metastasis. Open palliative surgery for pain, vertebral collapse and neurological deficits is a standard, although minimally invasive spine surgery using percutaneous pedicle screw fixation (PPSF) is considered a valid alternative [44].

Chi et al. performed a retrospective study to compare the effectiveness of PPSF without decompression versus debulking surgery in patients with unstable, metastatic spinal cord compression. The patient group receiving the minimally invasive approach PPSF followed by external beam radiotherapy demonstrated shorter operation time, shorter hospital stay and less blood loss than the debulking group [45].

---

#### Disclaimer

None.

---

#### Conflicts of interest

The author declares no conflict of interests.

---

#### Acknowledgments

None.

---

#### REFERENCES

- [1] Diamandopoulos A, Skarpelos A, Tsiros G. The use of the kidneys in secular and ritual practices according to ancient Greek and Byzantine texts. *Kidney Int* 2005;68:399–404.
- [2] Eknayan G. The kidneys in the bible: what happened? *J Am Soc Nephrol* 2005;16:3464–71.
- [3] Maio G. The metaphorical and mythical use of the kidney in antiquity. *Am J Nephrol* 1999;19:101–6.
- [4] Greydanus DE, Kadochi M. Reflections on the medical history of the kidney: from alcaeon of Croton to richard bright - standing on the shoulders of giants. *J Integr Nephrol Androl* 2016;3:101.
- [5] Ardalan MR, Shoja MM, Tubbs RS, Eknayan G. Diseases of the kidney in medieval persia—the hidayat of Al-akawayni. *Nephrol Dial Transplant* 2007;22:3413–21.
- [6] Almeida A, Lira R, Oliveira M, Martins M, Azevedo Y, Silva K, et al. Bone marrow-derived mesenchymal stem cells transplantation ameliorates renal injury through anti-fibrotic and anti-inflammatory effects in chronic experimental renovascular disease. *Biomed J* 2022;45:629–41.
- [7] Liu Y. Cellular and molecular mechanisms of renal fibrosis. *Nat Rev Nephrol* 2011;7:684–96.
- [8] Ding DC, Shyu WC, Lin SZ. Mesenchymal stem cells. *Cell Transplant* 2011;20:5–14.
- [9] Hsu RK, yuan Hsu C. The role of acute kidney injury in chronic kidney disease. *Semin Nephrol* 2016;36:283.

<sup>11</sup> <https://www.britannica.com/topic/Scientology/Organization-of-the-church>, last access 7/12/2022.

<sup>12</sup> <https://archive.org/details/dianeticssciento0000hubb/page/432/mode/2up>, last access 7/12/2022.

<sup>13</sup> <https://www.europeantimes.news/2022/02/scientologists-say-at-superbowl-you-can-rise/>, last access 7/2/2022.

<sup>14</sup> <https://orthobuzz.jbjs.org/2015/05/14/jbjs-classics-the-role-of-continuous-passive-motion-in-orthopaedics/>, last access 7/13/2022.

- [10] Ferenbach DA, Bonventre JV. Acute kidney injury and chronic kidney disease: from the laboratory to the clinic. *Nephrol Ther* 2016;12:S41.
- [11] Chang S, Chang M, Liu G, Xu D, Wang H, Sun R, et al. LncRNA OIP5-AS1 reduces renal epithelial cell apoptosis in cisplatin-induced AKI by regulating the miR-144-5p/PKM2 axis. *Biomed J* 2022;45:642–53.
- [12] Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. *Nat Rev Mol Cell Biol* 2020;22:96–118.
- [13] Zhang X, Wang W, Zhu W, Dong J, Cheng Y, Yin Z, et al. Mechanisms and functions of long non-coding RNAs at multiple regulatory levels. *Int J Mol Sci* 2019;20:5573.
- [14] Ghafouri-Fard S, Dashti S, Farsi M, Hussien BM, Taheri M. A review on the role of oncogenic lncRNA OIP5-AS1 in human malignancies. *Biomed Pharmacother* 2021;137:111366.
- [15] Yamada Y, Arai T, Kojima S, Sugawara S, Kato M, Okato A, et al. Regulation of antitumor miR-144-5p targets oncogenes: direct regulation of syndecan-3 and its clinical significance. *Cancer Sci* 2018;109:2919.
- [16] Fu W, Yu G, Liang J, Fan P, Dong K, Zhang B, et al. miR-144-5p and miR-451a inhibit the growth of cholangiocarcinoma cells through decreasing the expression of ST8SIA4. *Front Oncol* 2021;10:3104.
- [17] Uchida A, Seki N, Mizuno K, Misono S, Yamada Y, Kikkawa N, et al. Involvement of dual-strand of the miR-144 duplex and their targets in the pathogenesis of lung squamous cell carcinoma. *Cancer Sci* 2019;110:420–32.
- [18] Chen K-WK, Tsung-Ning Huang D, Huang L-M. SARS-CoV-2 variants – evolution, spike protein, and vaccines. *Biomed J* 2022;45:573–9.
- [19] Trypsteen W, White CH, Mukim A, Spina CA, de Spiegelaere W, Lefever S, et al. Long non-coding RNAs and latent HIV – a search for novel targets for latency reversal. *PLoS One* 2019;14:e0224879.
- [20] Liu X, Xu M, Li P, Zhang W, Zeng L, Yang Y, et al. Roles of lncRNAs in the transcription regulation of HIV-1. *Biomed J* 2022;45:580–93.
- [21] Clish CB. Metabolomics: an emerging but powerful tool for precision medicine. *Cold Spring Harb Mol Case Stud* 2015;1:a000588.
- [22] Sharpe RJ. The low incidence of multiple sclerosis in areas near the equator may be due to ultraviolet light induced suppressor cells to melanocyte antigens. *Med Hypotheses* 1986;19:319–23.
- [23] Harbo HF, Gold R, Tintora M. Sex and gender issues in multiple sclerosis. *Ther Adv Neurol Disord* 2013;6:237.
- [24] Gaitán MI, Correale J. Multiple sclerosis misdiagnosis: a persistent problem to solve. *Front Neurol* 2019;10:466.
- [25] Liu Z, Jeffrey W, Rui B. Metabolomics as a promising tool for improving understanding of multiple sclerosis: a review of recent advances. *Biomed J* 2022;45:594–606.
- [26] Ferraro F, Lo Celso C, Scadden D. Adult stem cells and their niches. *Adv Exp Med Biol* 2010;695:155.
- [27] Sagaradze G, Monakova A, Basalova N, Popov V, Balabanyan V, Efimenko A. Regenerative medicine for male infertility: a focus on stem cell niche injury models. *Biomed J* 2022;45:607–14.
- [28] Ng EH, Shah V. Guidelines for surfactant replacement therapy in neonates. *Paediatr Child Health* 2021;26:35–41.
- [29] Pérez-Gil J. A recipe for a good clinical pulmonary surfactant. *Biomed J* 2022;45:615–28.
- [30] Moulis G, Martin-Blondel G. Scrofula, the king's evil. *C Can Med Assoc J* 2012;184:1061.
- [31] Conde R, Laires R, Gonçalves LG, Rizvi A, Barroso C, Villar M, et al. Discovery of serum biomarkers for diagnosis of tuberculosis by NMR metabolomics including cross-validation with a second cohort. *Biomed J* 2022;45:654–64.
- [32] Gyawali B, Ramakrishna K, Dharamoon AS. Sepsis: the evolution in definition, pathophysiology, and management. *SAGE Open Med* 2019;7:205031211983504.
- [33] Pittet D, Allegranzi B. Preventing sepsis in healthcare – 200 years after the birth of Ignaz Semmelweis. *Euro Surveill* 2018;23:1.
- [34] Lin CY, Wang YH, Chen YM, Hung KY, Chang YC, Fang YT, et al. Dynamic monitoring of kidney injury status over 3 days in the intensive care unit as a sepsis phenotype associated with hospital mortality and hyperinflammation. *Biomed J* 2022;45:665–74.
- [35] Yang CK, Lee CY, Wang HS, Huang SC, Liang PI, Chen JS, et al. Glomerular disease classification and lesion identification by machine learning. *Biomed J* 2022;45:675–85.
- [36] Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim B, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet* 2017;389:1730–9.
- [37] Naik VN, Gamad RS, Bansod PP. Effect of despeckling filters on the segmentation of ultrasound common carotid artery images. *Biomed J* 2022;45:686–95.
- [38] Holley T. Auditing Scientology: reexamining the Church's 501(c)(3) tax exemption eligibility. *Tex Tech L Rev* 2022;54:345–79.
- [39] Klomjai W, Katz R, Lackmy-Vallée A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Ann Phys Rehabil Med* 2015;58:208–13.
- [40] Ni HC, Lin HY, Chen YL, Hung J, Wu CT, Wu YY, et al. 5-Day multi-session intermittent theta burst stimulation over bilateral posterior superior temporal sulci in adults with autism—a pilot study. *Biomed J* 2022;45:696–707.
- [41] Bar-On L, Molenaers G, Aertbeliën E, Van Campenhout A, Feys H, Nuttin B, et al. Spasticity and its contribution to hypertonia in cerebral palsy. *BioMed Res Int* 2015;2015:317047.
- [42] Salter R. The biologic concept of continuous passive motion of synovial joints. The first 18 years of basic research and its clinical application. *Clin Orthop Relat Res* 1989;242:12–25.
- [43] Chuang LL, Chuang YF, Jhu YJ, Hsu AL, Chen CL, Wong AMK, et al. Effects of ankle continuous passive motion on soleus hypertonia in individuals with cerebral palsy: a case series. *Biomed J* 2022;45:708–16.
- [44] Colangeli S, Capanna R, Bandiera S, Ghermandi R, Girolami M, Parchi PD, et al. Is minimally-invasive spinal surgery a reliable treatment option in symptomatic spinal metastasis? *Eur Rev Med Pharmacol Sci* 2020;24:6526–32.
- [45] Chi JE, Ho CY, Chiu PY, Kao FC, Tsai TT, Lai PL, et al. Minimal invasive fixation following with radiotherapy for radiosensitive unstable metastatic spine. *Biomed J* 2022;45:717–26.