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Highlights

Small and mighty – microRNAs pulling the strings

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ABSTRACT

The current issue of *Biomedical Journal* gives an insight into the influence miRNAs have in myocardial injury, and in hepatocellular carcinoma. Furthermore the association between dysmobility syndrome and vertebral fractures is assessed, the role of doxycycline in schistosomiasis is elucidated, and the effect of stress on the blood–brain barrier is examined. An article proving the accuracy of Taiwan's largest medical record databank is presented, as well as a potential biomarker for Parkinson's. Risk factors for recurrence of papillary thyroid cancer are identified, the outcome of reirradiation in oral squamous cell carcinoma is investigated, and the post-surgery outcomes in cases of infantile hypertrophic pyloric stenosis are reviewed. Finally this issue contains two articles about COVID-19, one describes the potential neurological damage left after the infection, and the second article analysis the outcome of uptake in vaccination against SARS-CoV-2.

Spotlight

From the Napoleon of neuroses to myocardial injury

The neurologist Jean-Martin Charcot received the nickname "Napoleon of neuroses" due to his considerable influence on the advancement of neurology, psychology and modern psychiatry in post-revolution France. Charcot replaced traditional rounds in the ward with shows, displaying patients with a group of symptoms termed hysteria. During Charcot's time hysteria was very *en vogue* and he would hence set up a stage for public clinical demonstrations, in which he would interview and hypnotize patients to perform theatrically[1] Various diseases were named after Charcot following his medical achievements.[1] Charcot-Marie-Tooth disease for instance is a neuropathy correlated to a mutation in apoptosis inducing factor mitochondria associated 1 (*AIFM1*) [2]. *AIFM1* encodes a mitochondrial flavoprotein that is essential for nuclear disassembly in apoptotic cells [3].

AIFM1 is involved in multiple diseases, and Zhou et al. set out to elucidate the underlying regulatory mechanism of AIFM1 in myocardial injury. The researchers studied the expression levels of AIFM1 *in vitro* and *in vivo*, and discovered that the protein negatively impacts myocardial ischemic injury. AIFM1 was furthermore upregulated which may be partly due to down-regulation of miR-145-5p [4].

The small noncoding microRNAs (miRNAs) are ubiquitously present in cells as regulators of gene expression. MiRNA biogenesis is controlled by numerous enzymes producing primary, precursor, and mature miRNA. The latter product originates from the 5′ or 3' arm of the precursor and is hence denoted with a -5p or -3p suffix respectively. One arm becomes functional by incorporation into the RNA induced

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[1] http://www.whonamedit.com/doctor.cfm/19.html, last access 11/16/2022

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silencing complex (RISC), whereas the other arm used to be considered a byproduct that would be degraded. Studies implicate though that both, the mature miR-5p and miR-3p pair, may co-exist and can be associated with RISC [5,6].

Co-existing miRNA pairs have been reported in different cancer cells [7], global downregulation of miRNAs affects many cellular processes such cell cycle, proliferation, differentiation, and apoptosis. However, miRNAs also emerged as potential therapeutic agents [8]. miR-145-5p for instance has been found to suppress proliferation, migration and invasion of gastric cancer epithelial cells [9]. Furthermore it has been suggested to effectively target podocyte essential genes, possible applications could include the extension of miRNA toxicity to other cell types [8].

On the other hand molecularly different tumors may be distinguished by their specific miRNA profiling in order to tackle diagnostic and therapeutic challenges [10]. In terms of efficient delivery of miRNAs to target tissues in the treatment of cancer, miRNA nanoformulations could be of service to achieve enhanced cellular uptake, bioavailability and accumulation at the tumor site [11].

CircRNA and miRNA

Circular RNAs (circRNAs) may act as miRNA sponges, but also exert a multitude of other biological functions like transcriptional regulation, protein templates, protein decoys, scaffolds and recruiters. CircRNAs are found in various species ranging from viruses to mammals. Their unique structure provides them with a longer half-life and higher resistance to RNAse in comparison to linear RNAs [12].

In this issue of the *Biomedical Journal* the reader gains insight into an article of Mao and team, who were interested in the mechanisms of circRNA circ_0091579 in hepatocellular carcinoma (HCC) progression. The circRNA exhibited oncogenic properties *in vivo* and *in vitro*, enhancing the malignant potential of HCC cells through the miR-136-5p/TRIM27 axis [13]. MiR-136-5p has received attention in past years for targeting genes and regulating pathways related to gastric cancer, breast cancer, glioma cells, colon cancer, and lung adenocarcinoma [14]. The tripartite motif (TRIM) family proteins have been reported earlier for their oncogenic roles in various cancers [15].

Preventing fragility fractures

miRNAs are most abundant within cells, however, they are also present outside of cells in extracellular vesicles or bound to specific proteins. They are then detectable in blood serum, urine or saliva. It has been shown that miRNAs affect bone homeostasis, including bone remodeling and fracture healing by alteration of gene expression in bone cells. Specific circulating miRNAs hence reflect the presence of osteoporotic vertebral fractures (VF) and could hence serve as a biomarker [16]. Fragility fractures (FF) are a main consequence of osteoporosis, and are often associated with severe pain, disability and death for the patients. FF can also become a substantial cost burden to the public health system. Preventive measures are therefore key [17].

Chen et al. headed out to determine a reliable method to predict prevalent VF as a vital step in early treatment of osteoporosis *inter alia* with the goal to prevent further fractures. The team assessed the connection between dysmobility syndrome (DS) and VF [18].

The term DS has recently emerged to describe an approach to evaluate the musculoskeletal health of elderly persons, so that that patient group can be targeted for timely interventions if need be. Classification parameters of the model are however not standardized, originally a score-based approach was proposed. DS is associated with reduced function, increased falls and fractures, and mortality. Also high body fat, osteoporosis, low muscle mass, low muscle strength, and slow gait speed are used in diagnosing DS [19,20]. (Fig. 1).

In their cross-sectional study, Chen et al. included fracture risk, bone mineral density, body composition, grip strength, walking speed and fall history. The team created a nomogram they propose as first-line prevalent VF screening method [18].

Also in this issue

Original articles

T-helpers in fluke infection

Upon antigenic stimulation by antigen-presenting cells, naïve CD4+ T-cells (Th0) differentiate into at least five effector cell subsets, comprising *inter alia* T-helper 1 (Th1) and T-helper 2 (Th2). Th1 cells are involved in cell-mediated immune responses such as macrophage activation, leading to the elimination of pathogens like Leishmania. Th2 cells promote a humoral immune response, and are associated with combating chronic infections and extracellular pathogens including helminths and nematodes. The Th2 response produces cytokines that dampen a Th1 response. Th1 cells have been associated with autoimmune disorders, whereas Th2 cells are shown to be critical in the development of allergic inflammation [21].

Souza et al. investigated the connection between lung inflammation caused by *S. mansoni* infection and administration of the antibiotic doxycycline (Dox) *in vivo* [22]. The acute and chronic parasitic disease schistosomiasis is a neglected tropical disease as categorized by the WHO. The larvae of the blood fluke causing the infection are released by freshwater snails and can penetrate skin during contact with infested water. Symptoms of schistosomiasis are caused by the body's reaction to the parasite's eggs.[2]

Souza et al. found that a higher dose of Dox aggravated lung granulomatous inflammation in a dose-dependent way. The team concludes this to be a result of the downregulation of Th2 effectors, as Dox reinforces Th1 cytokines [22].

The blood–brain barrier under stress

As a schoolboy the German physicist and scientist Paul Ehrlich was introduced into the secrets of cell staining by his cousin Karl Weigert, consequently developing a fascination that he retained for the rest of his life. Weigert was the first

[2] https://www.who.int/news-room/fact-sheets/detail/schistosomiasis, last access 11/10/2022

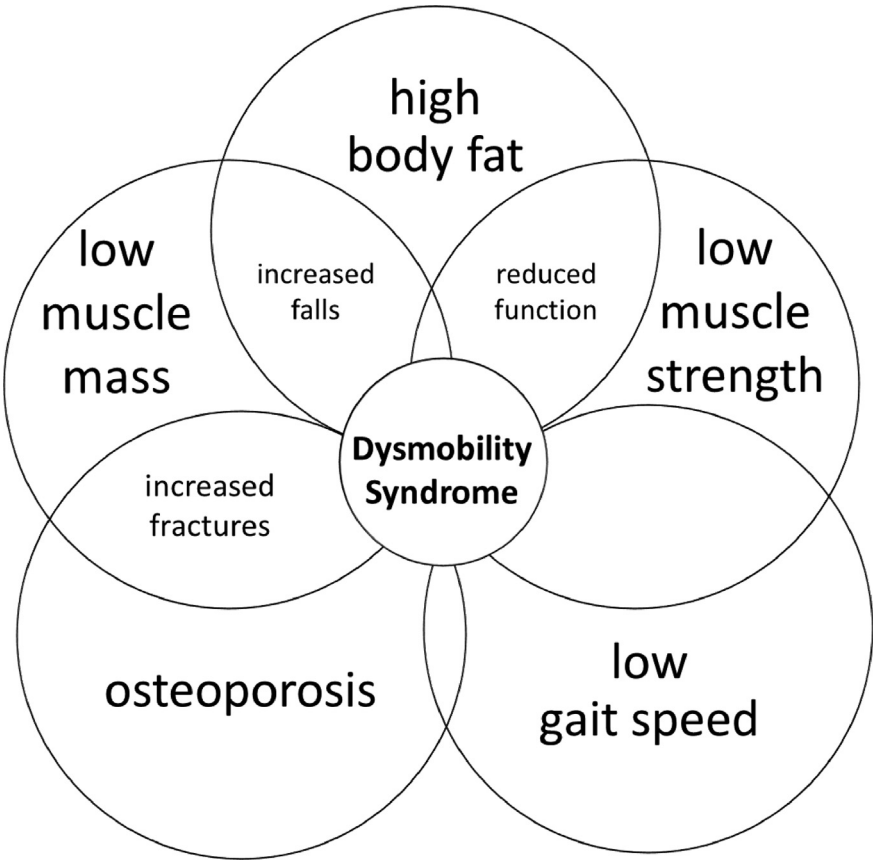

Fig. 1 Clinical risk factors for functional disability that are currently in use for diagnosis of dysmobility syndrome.

person to create a stain for bacteria, and later on the first to establish a protocol for staining myelin sheath.[3] With his doctoral dissertation Ehrlich contributed in a major fashion to the knowledge of histological staining techniques of his time. However, his thesis also made him unpopular as he was opening up a field between chemistry, biology and medicine that did previously not exist. Ehrlich's medical peers had difficulties following his thinking which was considered out of the box. The reason was the depth of chemical knowledge Ehrlich's studies would demand [23]. Ehrlich would foster the basis for modern hematology, and one of his staining experiments in the late 19th century led to the discovery of the blood–brain barrier (BBB) [24].

Since the BBB controls the influx and efflux of biological substances, it plays a critical role in maintaining the homeostasis of the brain environment [25]. Liao et al. showed that mice display disruption in BBB integrity as well as increased ventral hippocampal autophagic flux as an effect of stress while lacking of behavioral control [26].

Falling leaves

The Chinese idiom "falling leaves return to their roots" alludes to the desire of a person to return home, to their hometown or family.[4] It is also a widely distributed belief in the according cultural circle and affects the behavior of critically ill patients in hospitals. In order to maintain dignity and to make their own decisions, terminal patients of specific cultural backgrounds often decide to be discharged from the hospital to return home. They prefer to die in an environment that gives them the autonomy and privacy they desire [27].

The Chang Gung Research Database (CGRD) is considered the largest multi-institutional electronic medical record collection in Taiwan and hence frequently used to perform research studies [28]. Huang et al. aimed at validating the accuracy of the CGRD, especially focusing on the discharge status considering that terminally ill patients often choose not to stay in the hospital, hence mortality rate in the CGRD might be underestimated. The findings of the research team reported the discharge status registered in the CGRD to be highly accurate, the integration of a follow-up discharge status is however recommended [29].

An Italian city and the discovery of hereditary Parkinson

In 1986 the neurologist Larry Golbe, who specialized in Parkinson's, treated two brothers affected by the disease. Due to what he thought to be an unlikely coincidence, Golbe felt compelled to examine the rest of the brother's family as well, and found 6 more family members with symptoms of Parkinson's disease (PD). The family had their roots in the small Italian town Contursi Terme. A few months later Golbe diagnosed another patient with PD who had her origins in the same town [30]. There was no longer the question of

[3] http://www.paul-ehrlich.de/Teachers/weigert.htm, last access 11/12/2022

[4] https://blogs.transparent.com/chinese/chinese-idioms-vol-7/, last access 11/19/2022

coincidence, and eventually six families were found with 400 members over five generations, of which 60 were known to have had or to have PD. The family members were found to be the genetic offspring from one couple who lived during the 17th century in Contursi Terme.[5] A mutation in the α-synuclein gene was consequently identified in the Italian kindred with PD [31].

Chen et al. see an urgent need for a reliable biomarker to detect the neurodegenerative disease early. The team performed a study to investigate serum levels of phosphorylated α-synuclein protein, and showed that they potentially are a sensitive biomarker for clinical PD diagnosis [32].

Don't cu soon

Papillary thyroid cancer (PTC) is the most frequent form of all thyroid cancers and occurs predominantly in middle-aged adults with a 3:1 female to male ratio [33]. Thyroid cancer recurrence is associated with increased mortality as well as adverse outcomes overall, hence predicting recurrence risk poses a chief challenge in disease management [34].

In order to identify factors associated with PTC recurrence, Sun et al. retrospectively reviewed factors like demographic features, operation method, image character, therapeutic dose and more in over 800 PTC patients. The research team concluded that patients in early tumor-node-metastasis stages demonstrated lower recurrence rates than patients in advanced stage. Main risk factors for recurrence include distant metastasis, male gender, and a high serum thyroglobulin level [35].

A stimulant associated with carcinoma

Betel nut chewing has a long standing tradition in some South and South-East Asian regions, and would play a role in social customs, religious practices and cultural rituals. Betel nut acts as a stimulant, however, long-term use effects may include mouth and stomach ulcers, heart disease and oral cancers.[6]

Taiwan is one of the regions with widespread betel quid chewing as well as prevalence of oral cavity squamous cell carcinoma (OSCC). Chen et al. performed a retrospective study in 83 Taiwanese patients to predict the outcome of reirradiation (re-RT) for recurrent or new primary OSCC. The researchers identified a performance status and re-RT dose above 60 Gy as predictors for locoregional progression-free survival and overall survival (OS). Chen et al. suggest that surgery before re-RT might further enhance OS, and suboptimal re-RT results might be improved through combination with new therapeutic drugs or radioenhancers [36].

Gatekeeper

The rate at which alcohol is absorbed by the human body is influenced by various factors, and only a small fraction of ingested ethanol is cleared by first-pass metabolism. In a fasted state up to 96% of the ingested alcohol leave the stomach within a maximum of 23 min into the small intestine, where absorption happens almost instantaneously. In comparison, when ingested with a meal, ethanol disappearance from the stomach is significantly slowed down [37,38], leading up to a 50% relatively lower peak blood alcohol concentration.[7] One contributing factor in this case is the pyloric sphincter closing for digestion of the solid food [37].

Infantile hypertrophic pyloric stenosis (IHPS) consists of an abnormal thickening of the pylorus muscles. Infants are well at birth, but present three to six weeks after birth with projectile vomiting, potentially entailing dehydration and weight loss [39].

Chuang et al. examined the factors that affect the severity of pyloric hypertrophy, post-operative feeding, and nutritional recovery in IHPS. Their study indicates that nutritional outcomes were good with significant weight gain 6–8 weeks post-surgery [40].

Brief communication

Long-term neurologic damage caused by COVID-19

Akcay et al. discuss a pediatric case presenting pathological signal enhancement and edema in bilateral lentiform and caudate nuclei associated with COVID-19. The child in question had previously been healthy, and presented to the emergency department with fever, muscular weakness and a cough. It did not test positive for COVID-19 at that point, but later an antibody test provided prove of a SARS-CoV-2 infection. The research team shortly discusses the most frequent neurological manifestations associated with COVID-19, and the potential of the infection leaving permanent neurological damage [41].

Letter

COVID-19: does a specific vaccine formulation matter?

Mattiuzzi, Henry and Lippi refer to an article by Ysrafil et al. in which an increasing diversity in spike SARS-CoV-2 sequences worldwide was observed. Ysrafil and team consequently called for heightened consideration of geographic differences when it comes to vaccine development [42]. Mattiuzzi et al. emphasize that other aspects are likely to contribute to the differences seen in the risk of dying of COVID-19, such as demographic, economic, clinical and preventative or therapeutic factors. The analysis they performed demonstrated a linear association between averted deaths of older people from COVID-19 and vaccine uptake per country, independently of the vaccine formulation used against SARS-CoV-2 [43].

Disclaimer

None.

[5] https://blogs.unimelb.edu.au/sciencecommunication/2018/09/30/the-contursi-curse/, last access 11/19/2022

[6] https://adf.org.au/drug-facts/betel-nut/, last access 11/13/2022

[7] https://sites.duke.edu/apep/module-1-gender-matters/content/content-how-is-alcohol-absorbed-into-the-body, last access 11/13/2022

Conflicts of interest

The author declares no conflicts of interest.

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