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Highlights

Greek gods and the double-edged sword of liver regeneration

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ABSTRACT

In the current issue of the *Biomedical Journal* we gain an insight into the regeneration of liver tissue and how an over-the-counter supplement, stem cells and two plant extracts counteract liver damage. Furthermore the advances against hepatitis C virus are presented, the role of long non-coding RNA elucidated as well as the potential of an adhesion G protein-coupled receptor. In another contribution, the definition and evolutionary impact of copy number variants is clarified. Also, the polymorphism of a scaffolding caspase is investigated. We furthermore learn about the relation between SARS-CoV2 mutants in dependence of geography and explore the challenges of telemedicine in a complex healthcare field. A novel approach to engineering artificial grafts is presented, the challenges of total knee arthroplasty discussed as well as a possible mean of sinus floor elevation for dental implants. At last the concept of flipped classroom is scrutinized in terms of usefulness for a hospital in Taiwan.

Spotlight on reviews

Greek gods and the double-edged sword of liver regeneration

The giant Tityos counts as one of the three big villains in Greek mythology. Whereas Sisyphus is part of the trio because he tricked the god of the underworld, Tartarus is a personified part of the underworld itself. Tityos on the other hand is being punished for an attempted rape: he has to endure the torture

of a snake, alternatively two vultures, that consume his liver. The liver grows back every night^{1,2} and since Tityos is immortal, his pain never ends. Similarly, the Titan god Prometheus is punished for defying the king of the gods Zeus. Prometheus created humans out of water and earth and brought them fire against explicit interdiction of Zeus. Prometheus was celebrated as originator of human civilization, the punishment for his disobedience though was severe. According to Greek mythology Prometheus was chained to a rock

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¹ <https://www.theoi.com/Text/HyginusFabulae2.html>, last access: 10/03/2021.

² [https://www.journal-of-hepatology.eu/article/S0168-8278\(12\)00322-4/fulltext](https://www.journal-of-hepatology.eu/article/S0168-8278(12)00322-4/fulltext), last access: 10/03/2021.

where an eagle consumed his liver, all the same with the organ growing back every night.³

The regenerative abilities of the liver appear to have been known since antique times. However, within this ability also lies a double-edged sword. The regenerative mechanism by the means of hepatic progenitor cells that counteract mild to moderate liver damage can also be improperly activated. Abnormal activation is associated with fibrotic responses contributing to the development of liver cancer [1]. The final consequence of hepatic diseases is liver fibrosis. Currently, the only effective therapy is liver transplantation which comes with its own sets of challenges like availability of organ donors, cost etc. [2] [Fig. 1].

Since ancient times, the natural remedy *Silybum marianum* (milk thistle) has been used to alleviate various disorders associated with the liver. The major active compound silybin acts through modulating inflammation and apoptosis in combination with providing antioxidant power [3].

Resveratrol is an antimicrobial compound produced by more than 300 edible plants as a response to biotic and abiotic stress. It has many therapeutic effects and a positive effect on liver disorders has been demonstrated in various studies [4,5].

Khalil et al. set out to evaluate the therapeutic effect of bone marrow mesenchymal stem cells (BM-MSCs) in comparison to *S. marianum* and resveratrol on carbon tetrachloride induced liver fibrosis in male rats. They conclude that the approach with BM-MSCs is more efficient than the two aforementioned plant extracts. This is due to the stem cells' unique abilities in terms of self-renewal and multipotent differentiation. The analysis reveals a significant reduction in stiffness as well as roughness in fibrotic livers after treatment with BM-MSCs [2].

An OTC supplement with considerable potential

Tissue damage in the liver ensuing cell apoptosis is not only induced by lifestyle choices, the exposure to toxins and xenobiotics but also by alcohol and medications [6].

Methotrexate (MTX) is part of the WHO's list of essential medicines and used as an effective treatment against autoimmune and inflammatory disorders. It acts by interfering with the folic acid metabolism, thus blocking tetrahydrofolate synthesis and finally DNA biosynthesis. MTX is hence applied against various types of cancers since it leads to the inability of cells to divide and produce proteins. However, its low-dose application is associated with hepatotoxicity, pulmonary toxicity and bone marrow disorders. Nephrotoxicity, hepatotoxicity, neurotoxicity are *inter alia* associated with high-dose application of the drug [7,8].

MTX is thought to induce hepatic damage through reactive oxygen species (ROS). Mehra et al. hence performed an *in-vitro* and *in-vivo* study to assess the cyto-protective effects of alpha-ketoglutarate (AKG). The supplement can be bought OTC. It is used to enhance athletic performance and scavenges ROS.

Mehra et al. demonstrated for both study settings the hepatoprotective ability of AKG, thus setting the basis to validate those findings in humans [9].

On the way to eliminate one public health issue at a time

Just recently, for the first time, the WHO released guidelines on the hepatitis C virus (HCV) self-testing. This initiative adds to the goal to eliminating HCV as a public health issue by 2030.⁴ Although 30% of newly infected persons spontaneously clear the virus through a strong immune response, the remaining 70% require treatment due to development of a chronic infection and potentially liver cirrhosis.⁵

In their review Lin et al. honor the substantial contribution made by 2020 Nobel Prize laureates Harvey J. Alter, Michael Houghton and Charles M. Rice in the fight against HCV [10]. Chronic HCV infection is a leading cause for liver-related death, but thanks to a new generation of direct acting agents (DAAs), the pitfalls of past treatment strategies are avoided [11]. The development of DAAs was largely enabled through the decade-lasting combined research of the physician, the molecular biologist and the virologist who shared the Nobel Prize for their breakthrough work [10]. DAAs cure 95% of people infected with HCV, depending on the degree of liver tissue damage. A troublesome prerequisite for people who are often asymptomatic though remains in the access to diagnosis as well as to the treatment itself.⁶ The self-testing guidelines were established in an effort to close this gap further.

Also in this issue

Reviews

One man's junk is another's treasure

Non-coding RNAs (ncRNAs) used to be dismissed as junk RNA since they cannot be translated into a protein. However, it has been demonstrated that ncRNAs are involved in numerous physiological and pathological processes.

Through interacting with proteins, RNA and DNA long non-coding RNA (lncRNA) serves as signal, decoy, guide and scaffold, thus affecting and regulating gene expression. LncRNAs are closely associated to the occurrence and development of various cancers [12] and their expression is cell-type specific [13].

Peng et al. reviewed the role of lncRNA in relation to hypoxia, a known factor fostering tumor metastasis. They illustrate how lncRNAs can serve as diagnostic and prognostic marker for various human cancers and propose potential methods targeting lncRNAs as means of treatment [14].

⁴ <https://www.who.int/news/item/15-07-2021-who-releases-first-guidelines-on-hepatitis-c-virus-self-testing>, last access: 10/03/2021.

⁵ <https://www.who.int/news-room/fact-sheets/detail/hepatitis-c>, last access: 10/03/2021.

⁶ <https://www.who.int/news-room/fact-sheets/detail/hepatitis-c>, last access: 10/03/2021.

³ <https://www.perseus.tufts.edu/hopper/text?doc=Perseus%3Atext%3A1999.04.0104%3Aalphabetic+letter%3DP%3Aentry+group%3D47%3Aentry%3Dprometheus-bio-1>, last access: 10/03/2021.

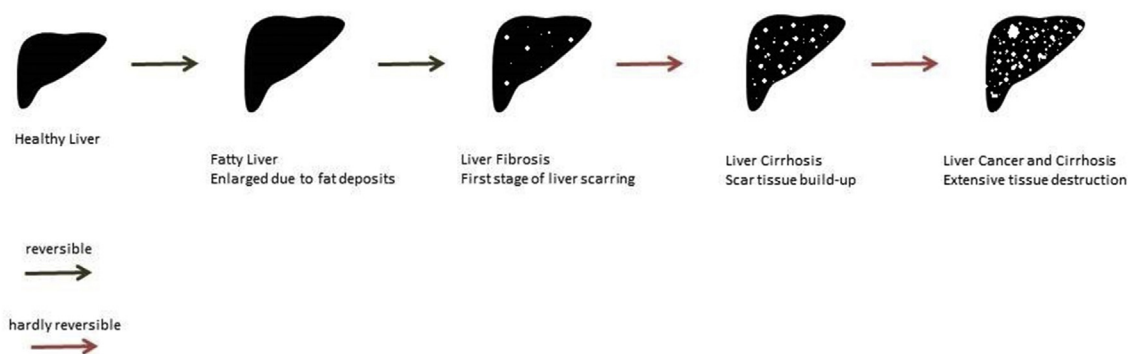


Fig. 1 Stages of liver damage. As the severity of liver damage and scarring progresses, regeneration of the liver is hardly possible anymore.

A large family of mediators

The largest class of transmembrane receptors are G protein-coupled receptors (GPCRs) with more than 800 of its kind in humans. They are subdivided into six classes, thus affecting a plethora of possible signaling cascades and therefore constitute unique potential drug targets. Adhesion GPCRs (aGPCRs) are distinguished by their large extracellular region with a variety of adhesive subdomains [15]. aGPCRs are considered to be evolutionary ancient and possess a conserved auto-proteolysis inducing domain called GAIN [16].

In their review Singh et al. comprehensively compile the current understanding of the role of the aGPCR GPR56 and the gene ADGRG1. GPR56/ADGRG1 play a role in the central and peripheral nervous system, immune system, hematopoietic cells, reproductive system and muscular hypertrophy. As such, the receptor is also involved in abnormal functioning of the nervous system as well as cancer development. GPR56 is consequently an important target for developing diagnostic tools and therapeutics [17]. A recent study for example showed that chronic, stress-induced downregulation of GPR56 leads to depression with suicidal tendencies and poor or no response to treatment with antidepressants. However, treatment of GPR56 knockdown mice with GPR56 peptide agonists demonstrated an antidepressant-like effect [18].

The cost of diversity

Copy number variations (CNV) contribute largely to population diversity. The underlying mechanisms include nonallelic homologous recombination, nonhomologous end-joining, and retrotransposon as well as fork stalling and template switching. CNVs may encompass repetitions in a part or all of a gene or a segment including several genes [19]. At the same time CNVs may cause a higher susceptibility to infectious disease and genetic disorders [20,21]. On that account they may also serve as biological markers. Pös et al. composed an extensive review concerning the definition of CNVs and the factors involved in their formation and evolutionary impact. Pös et al. advocate clearly defining CNVs in order to fully explore the insights various forms of polymorphism offer to scientific research [22].

Cards and microorganism – a bond throughout ages

Playing cards are thought to be originating in Asia, possibly in China around the 9th century AD. Card decks evolved over

time in their design and new games were invented as cards became more popular.⁷ Still existing everyday idioms like “on the cards”, “putting the cards on the table” etc. reflect the influence card games had on society. Interestingly, card games underwent tremendous popularity during times of pandemics. Playing at home with the family was a welcomed distraction and often games were also invented to reflect the challenges of the according era.⁸

The cards are stacked against pathogenic microorganisms when the scaffold protein Caspase recruitment domain-containing protein 9 (CARD9) comes into play. CARD9 is predominantly expressed in myeloid cells, acting as a link between innate and adaptive immunity. Its signaling through pattern recognition receptors (PRRs) leads to the activation of NF- κ B and MAPK and subsequently production of proinflammatory cytokines. CARD9 plays a role in the recognition of pathogenic microorganisms, especially fungi [23].

Ji et al. review currently known CARD9 mutations in order to elucidate the correlation between CARD9 polymorphism and disease risk in terms of inflammation, autoimmunity, fungal infection and inflammatory bowel disease. They present a potential mechanism for CARD9 polymorphism and conclude that CARD9 deficiency is caused by a multitude of possible mutations. Ji et al. see a necessity for more research in order to better understand which mutations are correlated to which clinical phenotypes [24].

Original articles

SARS-CoV2 mutants and geographical particularities

The spike protein of the SARS-CoV 2 mediates receptor binding and thus the fusion of viral and cellular membrane. Mutations of this protein have been gradually showing up over the development of the COVID-19 pandemic and are suggested to offer fitness advantages to the virus for instance in terms of transmission [25]. It has been suggested that geographical, climatic and sociodemographic factors impact the infection of the population with the virus [26]. The

⁷ <https://playingcarddecks.com/blogs/all-in/history-playing-cards-modern-deck>, last access: 10/03/2021.

⁸ <https://blog.shuffledink.com/card-games-created-during-pandemics/>, last access: 10/03/2021.

variance in case fatality rate (CFR) caught the attention of Ysrafil et al. who performed an analysis of the sequences of the spike proteins from patients in five different geographic areas. The correlation between the mutation distribution and the respective impact revealed that specific mutations lead to a higher CFR. Ysrafil et al. hence suggest that the prevalence of different mutations might require the development of vaccines on a country-by-country basis [27].

At your service

With the ongoing COVID-19 pandemic the need for novel means to providing patient care remains highly prevalent. With an increasing rate existing telemedicine and software platforms were applied in larger settings over the past two years to safely deliver healthcare to patients, while making efficient use of available medical resources [28].

Wu et al. performed a retrospective cohort study, looking at the usefulness of telemedicine under infectious conditions in otolaryngology outpatient consultations at a clinic in Taiwan. 2018 legal amendments were performed to further introduce telemedicine in the country, although it has not yet been largely included in otolaryngology routine clinical practice [29]. While on the one side healthcare can be made more accessible through telemedicine, disadvantages lie in the challenges of the technology itself. Technical knowledge, availability of a broadband connection and according devices as well as technological compatibility and cognitive and sensory impairments need to be considered [30]. Wu et al. conclude that remote, face-to-face, real-time otolaryngology telemedicine service is efficient, time-saving and satisfactory for patients as well as healthcare practitioners despite the limiting but often required specialized procedures in the field. Further technological progress will allow a higher patient eligibility and service level [29].

Building on the knowledge of the ancestors

For the first time and after decades of discussion across the U.S., a presidential proclamation has been issued concerning the Indigenous Peoples Day (formerly Columbus Day). The national holiday had been established in 1934 and by renaming it, an open concession is made to recognize Native Americans and their historical and cultural impact.^{9,10}

The knowledge about and medical application of traditional plants is one heritage of Native American tribes. Wintergreen is such an example. Its leaves were traditionally used against various ailments, the oil has later found wide application as aromatic in food and cosmetic products [31]. Due to its unique medicinal features Eldurini et al. made use of wintergreen oil for the development of an artificial vascular graft [32].

Several obstacles have to be defeated in the quest for the ideal, artificial vascular graft. The grafts need to be of small diameter while proving to strong, flexible, anti-kinking and anti-thrombogenic at the same time [33].

Electrospinning is technique that has been re-invented in the 1990s after decades of stagnancy. Electrospinning polymers into nanofibers was confirmed to meet the challenging requirements of successful tissue engineering [34]. To overcome the limitations like bioactivity and hydrophobic nature of the materials used, the technique has been further developed and modified for instance by embedding living cells into the electrospun fibers [35].

Eldurini et al. opted to coat electrospun polycaprolactone fibers with polyethylene oxide and the natural essential oil wintergreen in order to develop a multifunctional vascular scaffold. Their grafts exhibited a satisfying bio-compatibility, requiring however further assessment to optimize the construction [32].

To knee or not to knee

As a consequence of renal osteodystrophy, steroid use, amyloid deposition and immunosuppressive therapy after renal transplant, patients with end-stage renal disease (ESRD) have an increased risk of osteonecrosis and osteoarthritis [36]. Accordingly full hip replacement and full knee replacement are more often required in this patient group than in the general population [37]. It has been shown that total knee arthroplasty (TKA) leads to high patient satisfaction regarding quality of life and pain relief [38], although ESRD on its own is a risk factor for perioperative complications [36,37,39,40].

Lee et al. retrospectively evaluate the outcomes of total knee arthroplasty (TKA) with and without end-stage renal disease (ESRD) in Taiwanese patients over the timespan of seven years. They conclude that due to the complications, increased mortality rate as well as costs, the risks versus benefits of TKA in ESRD patients have to be thoroughly considered [41].

The tooth fairy always comes twice

The tooth fairy is known across various cultures worldwide. Usually the folklore tale involves a fairy, a mouse or angels that offer money or gifts in exchange for a tooth a child loses [42]. As humans lose their teeth a second time, the consequences are usually less rosy. Dimensional changes of hard and soft tissues occur, complicating the installation of an implant in these sites [43]. The volume increase of the paranasal sinus known as maxillary sinus pneumatization may lead to the union of the sinus floor and the crest of the remaining bone after posterior tooth extraction [44]. The different surgical approaches employed in order to augment the maxillary sinus floor offer various advantages and disadvantages [45]. Furthermore, the grafting material has an essential influence on the functional load of the bone surrounding the implant. Kuo et al. investigated the stability of synthetic biphasic calcium phosphate in bone-added osteotome sinus floor elevation (BAOSFE). They determine that transcrestal sinus floor elevation with the alloplastic material allows for a predictable modality, although individual prerequisites of the graft influence the outcome [46].

Turning conventions upside down

Conventional classroom teaching puts the teacher into the center and the student into a more passive role. The material is introduced in the classroom and then deepened by the

⁹ <https://www.denverpost.com/2021/10/11/columbus-day-indigenous-peoples-day/>, last access: 10/03/2021.

¹⁰ <https://eu.usatoday.com/story/news/nation/2021/10/11/indigenous-peoples-day-everything-you-need-know-holiday/6087138001/>, last access: 10/03/2021.

student at home. In the flipped classroom (FC) concept, the students actively execute the pre- and post-class activities on their own. The in-class time is then used for interaction to establish a habit of self-directed learning as well as higher cognitive learning. Hereby the facilitator mainly acts as a guide and monitor [47]. The hybrid model incorporates online activities with face-to-face classroom time. The outcome varies from students learning faster and more efficiently with this model to students performing less well than in a traditional classroom set-up [48].

Chen et al. were interested on the effectiveness of the program *Teaching on the Run* (TOTR) that is based on an Australian model of the FC. They performed a retrospective before-after study at a hospital in Taiwan where the model had been introduced in 2014. Chen et al. concluded, that facilitators should strive to include more pre-class learning and engagement in classroom activity to achieve better learning gain [49].

Conflicts of interest

The author declares no conflict of interests.

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