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Highlights

A finger in every pie – The versatility of chemokines

Aila Akosua Kattner*

Freelance Journalist, Berlin, Germany

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ABSTRACT

In this issue of Biomedical Journal we encounter the chemokine superfamily and its clinical potential. The time course from 56 days zero COVID-19 to a resurgence in cases is presented, as well as a possible solution to overcome rejection in vascularized composite allotransplantation. We are shown the opportunity deep learning (DL) offers in the case of tracking single cells and particles, and also use of DL to bring all hands on deck to counter the current challenge of the COVID-19 pandemic. This issue contains articles about the effect of low energy shock waves in cystitis; the negative effect of high fructose on aortic valve stenosis; a study about the outcome of fecal microbiota transplantation in case of refractory *Clostridioides difficile* infection; a novel long non-coding RNA that could serve in treating triple-negative breast cancer; the benefits of acupressure in patients with restless leg syndrome; and Filamin A mutations in abnormal neuronal migration development. Finally, a link between jaw surgery and the psychological impact on the patient is explored; a method presented that allows identification of cervical characteristics associated with difficult embryo transfer; and a letter suggesting new parameters to evaluate the use of bone-substitute augmentation in the treatment of osteoporotic intertrochanteric fractures.

Spotlight

The chemokine superfamily comprises a number of ligands and receptors that appear to be redundant at first with promiscuous ligand–receptor relationships. However, as to be expected, the system is far more complex. Inflammatory chemokines play a major role in the organization of the immune system, mainly attracting macrophages or neutrophils. Homeostatic chemokines are considered chemotactic master regulators in the movement and localization of cells involved in acquired immunity like lymphocytes and dendritic cell subsets in the body [1]. Chemokines may also stimulate a

number of undirected migratory behavior [2]. Chemokine receptors are a superfamily of G-protein-coupled receptors, some of them are rather promiscuous whereas others exhibit very restricted ligand–receptor relationships [1]. The selectivity is an intrinsic property of the chemokine–receptor pair itself, namely their amino acid sequence [3].

Chemokines are also involved in embryonic development and pathobiology of autoimmune diseases, tumorigenesis and metastasis. Some display an antimicrobial effect or are expressed in healthy tissues where they maintain immune functions such as leukocyte homing to the bone marrow [3–6]. [Fig. 1].

* Corresponding author. Freelance Journalist, Berlin, Germany.

E-mail address: aila.kattner@gmail.com.

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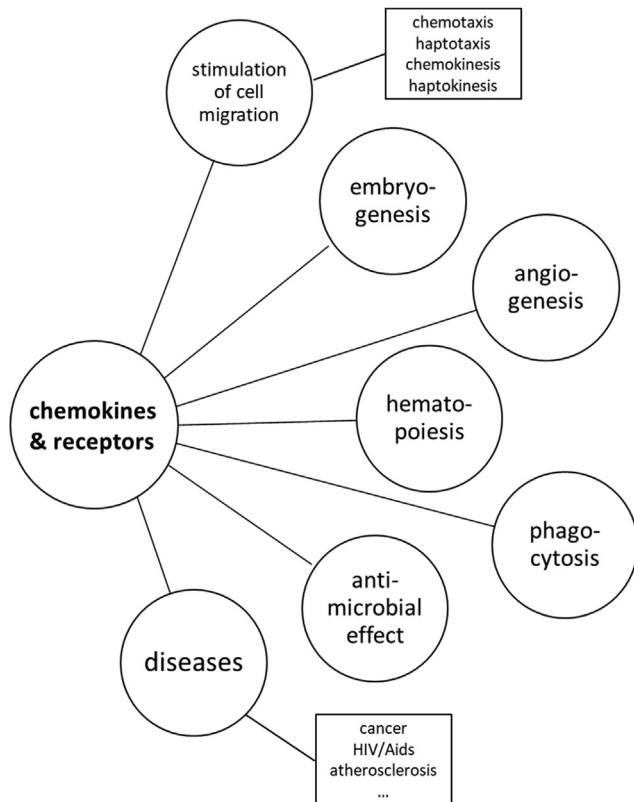


Fig. 1 Excerpt of chemokine involvement in physiological and pathological processes. Although chemokines and their receptors are often known for their chemotactic role in immune cell migration, they are additionally playing a role in numerous activities beyond the immune system.

Counterstrategy of the dark matter of biology

Since chemokines may act as chemotactic cytokines involved in directing cell migration, they play a crucial role in the antiviral immune response. Functions include binding leukocytes, activating a signaling cascade in the leukocyte influencing its arrest, crawling and transmigration [7].

Arthropods are part of almost every kind of parasitic relationship since they are either parasites themselves or function as host/vector for other micro-organisms.¹ In the latter case, it is suggested that they contributed in a major fashion to virus evolution. Viruses can be difficult to detect, and are hence at times jokingly called the “dark matter of biology”. Large-scale sequencing of genetic material from the environment mainly reveals the numerous diversity of viruses. However, the performance of metagenomic sequencing on a selection of arthropods for instance led to a new understanding of the depth and breadth of negative-sense RNA viruses that may cause influenza, Ebola, rabies and more [8]. In order to maintain virulence, some viruses, as well as parasitic arthropods, have developed a systematic counterstrategy with the help of chemokine binding proteins (CBP) [7,9].

¹ <https://parasite.org.au/para-site/contents/arthropod-introduction.html>, last access 05/20/2022.

Stark et al. reviewed the group of CBP focusing on those expressed by mammalian viruses. Understanding CBP better potentially opens the door to the development of anti-inflammatory agents that could for instance incapacitate inflammatory chemokines. Stark and her team furthermore present the opportunity computational simulation offers, allowing a deeper understanding of protein–protein interactions [9].

Another chemokine presented in this issue of *Biomedical Journal* is the homeostatic chemokine Stromal cell-derived factor-1 α (SDF-1 α). SDF-1 α is expressed in various organs and is *inter alia* associated with heart failure and all-cause mortality risk [10]. It has been suggested as a potential biomarker for hyperlipidemia since it plays a pivotal role in the mobilization of hematopoietic stem and progenitor cells in bone marrow [11].

Esophageal squamous cell carcinoma (ESCC) is considered one of the most deadly forms of human malignancies due to late state diagnosis, metastasis, therapy resistance and frequent recurrence [12].

Chen et al. performed a study that demonstrated how periodic determination of SDF-1 α serum level may serve as a valuable to predict prognosis of ESCC in patients receiving definitive concurrent chemoradiotherapy [13].

Also in this issue

Reviews

From 56 days zero COVID-19 to resurgence

In June 2020, after implementation of stringent non-pharmaceutical in China to prevent resurgence of SARS-CoV-2, a new case emerged. After 56 days of a zero new case interval, a man from Beijing with no exposure history to COVID-19 infected individuals was diagnosed with COVID-19. It has been suggested that the resurgence was likely initiated by an environment to human transmission originating from contaminated imported food via cold chain logistics [14].

Chen et al. set out to describe the time course and epidemiological features connected to cold-chain food or packaging contamination transmission leading to resurgence of COVID-19 in China. They advise for continuing to regularly test high-risk populations as well as imported cold-chain products. Additionally, strict compliance to procedures like proper disinfection of imported products is considered key [15].

An ancient miracle and its modern challenges

The miracle of the black leg performed in the 3rd century by the Saints Cosmas and Damian, two highly skilled doctors of a then Roman province of Syria, attests the first allotransplantation. Cosmas and Damian were called the Unmercenarys as they would not accept payment for their highly sought after services. The transplant of the leg of an Ethiopian man onto the body of a man with white skin inspired numerous artists to depict the “miraculous” scene [16].

Allograft rejection however poses a threat to achieving a successful vascularized composite allotransplantation (VCA). Unlike solid organ transplantation, VCA contains multiple tissue types including skin, muscle, bone, vessel and nerve. It poses a reliable treatment approach for patients who

underwent significant tissue loss. Anggelia and team review the current use of cell therapy to improve allograft outcome, and conclude that the suitable type of therapy is clinically dependent for instance on the allograft phase [17].

The children of HAL 9000

The New-York based, Serbian conceptual and performance artist Marina Abramovic created the project “In Residence”, which makes the public part of the performance. Each visitor sits down at an individual table and receives a mixed pile of rice and lentils, that needs to be sorted and counted by kind.²³ Abramovic describes the different phases the mind goes through during this endeavor. One essential step consists in the mind automatically reverting to creating a system in order to facilitate tracking each grain in a pile of thousands of grains, and finally clustering them by numbers. The artist herself uses this method on a regular basis to streamline her mind and prepare herself for her performances.⁴

In the machine world deep learning (DL) could be considered as an equivalent. DL is a machine learning technique teaching a computer to do what is natural to humans: learning by example. A computer model acquires the ability to perform classification tasks. With this mode of learning it can achieve surprisingly high levels of accuracy that even exceed human-level performance at times.⁵

Deep learning technologies are for instance contributing to advancements in solving problems in single cell tracking (SCT) and single particle tracking (SPT). Cheng et al. review current methods and tools in SCT and SPT, pointing out the issues raised by those methods and proposing future research trends [18].

Original articles

The grandchildren of HAL 9000

HAL 9000 (Heuristically programmed Algorithmic computer) is a character in the novel “2001: A Space Odyssey”. HAL is an artificial intelligence who becomes a main antagonist of the plot by progressively learning how to read and manipulate humans, while the system itself develops into a neurotic humanesque personality.⁶

Deep learning contributes in a major fashion to developing machine learning and according problem solving skills, as previously described. Specific advanced algorithms like a self-attention structure allows deep learning to correlate information by predicting or inferring elements.⁷

² <https://www.smh.com.au/entertainment/art-and-design/what-counting-3987-grains-of-rice-with-marina-abramovic-taught-me-20150623-ghvdrd.html>, last access 05/22/2022.

³ <https://www.smh.com.au/entertainment/art-and-design/marina-abramovic-in-residence-a-miraculous-respite-from-the-stresses-of-life-20150623-ghvrlz.html>, last access 05/22/2022.

⁴ <https://www.youtube.com/watch?v=472JcpWkWws>, last access 05/20/2022.

⁵ <https://uk.mathworks.com/discovery/deep-learning.html>, last access 05/24/2022.

⁶ https://2001.fandom.com/wiki/HAL_9000, last access 05/29/2022.

⁷ <https://lilianweng.github.io/posts/2018-06-24-attention/>, last access 05/29/2022.

Wang and team developed a novel natural language processing method to sift through the clinical research concerning COVID-19. The goal was to automatically recognize associations among different topics like the potential targeted host organ systems, associated clinical manifestations and pathways. Wang et al.’s bioinformatics approach is based on a deep learning framework with a state-of-the-art algorithm that provides a powerful self-attention structure. The research team’s method allowed to successfully identify hidden relationships through mining the available literature. Furthermore Wang et al. were thus able to point to several potential drug candidates that could serve in the future in managing COVID-19 [19].

Shock waves against bladder inflammation

Low-energy shock waves (LESWs) are used as therapeutic means to accelerate the healing of a variety of tissue injuries like bone fractures, and even including angiogenesis. It is suggested that mechanosensing is an underlying mechanism [20]. LESW facilitates tissue regeneration while additionally exerting an analgesic as well as anti-inflammatory effect [21].

Wang et al. examined the effects LESW exerts on bladder and mitochondrial function in rat model induced cystitis. The team suspected that dysregulation of mitochondria function contributes to bladder dysfunction in patients with interstitial cystitis/bladder pain syndrome. Their findings provided support for the anti-inflammatory effect of LESW in chemical cystitis [22].

The peril of high fructose

Metabolic Syndrome (MetS) is a pathological condition usually characterized by insulin resistance, high blood glucose, low level of HDL cholesterol, abdominal obesity, hypertension and hyperlipidemia. MetS is considered a major health hazard of the modern world [23]. It adversely influences several body systems, contributing to microvascular damage, vascular resistance, vessel wall inflammation, atherosclerotic disease, structural or ischemic heart disease, and other cardiovascular diseases [24].

MetS is a major risk factor of aortic valve stenosis (AS), however, overconsumption of fructose tops MetS as a risk factor. Chang et al. were interested to see, whether fructose consumption under physiological level induces AS. They co-cultured human valve interstitial cells in various concentrations of fructose and monitored and examined the concomitant expression of various proteins, including osteogenic and fibrotic proteins, as well as PI3K/AKT signaling. The results imply that even at physiological level high fructose fosters the progression of AS [25].

Fecal microbiota transplant as salvage therapy

Refractory *Clostridioides difficile* infection (rCDI) is associated with a high mortality rate and 30% of patients with severe infection require surgical intervention. However, the success rate of colectomy in that patient group is difficult to predict, and the surgical approach may have a poor outcome in patients with rCDI due to underlying medical conditions, leading to post-surgical mortality of 30–50%. Fecal microbiota transplantation (FMT) can be considered as salvage therapy, producing rates of cure in the range of 70–90% [26].

Yeh et al. studied the outcome of fecal microbiota transplantation (FMT) in Taiwanese patients with rCDI. They performed 16S rRNA sequencing of samples for donor and recipients before and after FMT, and found a success rate of 89.7% of the treatment with this approach [27].

A promising long non-coding RNA

LINC01559 is an novel, intergenic, long non-coding RNA (lncRNA). So far it has been shown to take part in promoting gastric cancer as well as the progression of pancreatic cancer, lung cell proliferation and migration through enhancing autophagy [28].

Yang et al. were particularly interested in exploring the role of LINC01559 in triple-negative breast cancer (TNBC). The team observed a significant increase of the lncRNA in TNBC tissues with LINC01559 functioning as carcinogenic competing endogenous RNA. Since TNBC tends to have a poor prognosis due to its heterogeneity as well as malignancy, LINC01559 could be a promising potential biomarker in TNBC treatment [29].

Can't get no sleep

Restless leg syndrome (RLS), the irresistible urge to move the legs, was first described in 1672 by an English physician with the words “the diseased can no more able to sleep, than if they were in a place of greatest torture”.⁸ RLS can frequently occur in hemodialysis patients. The pathophysiology is unclear, however, altered transferrin expression, and increased glutamate levels in the brain as well as imbalances in opioid receptors, the dopamine system, calcium/phosphate levels and single nucleotide polymorphisms might be contributing factors. RLS may severely disrupt sleep and furthermore impair quality of life in general [30].

Tsai et al. performed a 4-week crossover pilot study to research the effect of acupressure on sleep quality in hemodialysis patients with RLS. They found that the severity of RLS was alleviated through acupressure although no improvement of sleep quality could be observed. This however contradicts previous case reports and studies, and the team suspects that the contradiction might be caused by insufficient duration of acupressure application in their study [31].

Linking actin filaments

The homodimeric protein Filamin A (FLNA) associates with actin filaments, linking platelet cytoskeleton to other structural/signaling proteins and membrane receptors [32]. It is hence playing a role in processes such as cell migration, coagulation and angiogenesis. FLNA mutations have been observed in cases of X-linked periventricular nodular heterotopia (PVNH), an abnormal neuronal migration development [33].

Lu and team identified FLNA mutations in PVNH patients to delineate the clinical and imaging spectrum differentiating FLNA-positive and FLNA-negative patients [34].

The psychological effect of jaw surgery

Orthognathic surgery (OGS) is the treatment of choice for patients that are too old for growth modification, and also for dentofacial conditions considered too severe for surgical or orthodontic camouflage. In order to achieve a successful outcome of the procedure, close collaboration between the surgeon and the orthodontist across all stages of the treatment is vital [35]. Unfavorable outcomes may be caused before or during treatment and relate to both aesthetics and function, including unrealistic expectations of the patient, lack of understanding of treatment objectives or lack of clinical evaluation [36]. Surgery outcome of may severely influence a patient's self-perception. If a dentofacial deformity is subjectively perceived as a handicap, OGS could for instance wield a positive impact on the psychological perception of the patient [37].

Lin et al. performed a study to elucidate the short-term and long-term psychological impact and quality of life of OGS. They found that in both cases patient satisfaction was generally high, although aspects like deterioration in sleep and other limitations after OGS should be monitored and addressed to keep patient satisfaction high [38].

Difficulties with ETs

Embryo transfer (ET) is one of the most critical steps in in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI), although the success of the procedure depends on several factors like age of the woman, stimulation protocol and number of good quality embryos transferred. Difficulties in ET may have different origins, that each influence the procedure to a varying degree [39].

In order to examine the relationship between cervical finding under flexible outpatient hysteroscopy (OH) and difficult ET, Ou et al. performed a cohort study with 650 patients undergoing IVF/ICSI. The team was looking for the most appropriate diagnostic test to routinely assess uterine cavity before IVF ET. The team's study confirmed that OH allows to successfully identify cervical characteristics associated with a high incidence of difficult ET [40].

Letter

Setting new parameters to avoid misinterpretation

Hatano et al. refer to a previous article by Chang et al. [41] where the latter presents bone-substitute augmentation (BSA) as means to prevent excessive sliding of a lag screw in the treatment of osteoporotic intertrochanteric fractures. Hatano et al. question the effectiveness of the procedure as the reason for the sliding resides in poor bone contact and alignment according to their view. The team furthermore considers the method of analysis used to evaluate the outcome as insufficient and proposes the inclusion or alternative use of measures they consider more suitable. According to Hatano et al. it would thus be possible to avoid misinterpretation of the findings of Chang and team's study [42].

Conflicts of interest

The author declares no conflicts of interests.

⁸ <https://veincenternorthtexas.com/rls-history.html>, last access 05/28/2022.

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