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Highlights

Guards! Guards! How innate lymphoid cells ensure local law and order

Sophia Julia Häfner*

University of Copenhagen, BRIC Biotech Research & Innovation Centre, Lund Group, Copenhagen, Denmark

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ABSTRACT

This special issue of the *Biomedical Journal* is dedicated to the latest official recruits in the field of immunology: innate lymphoid cells, the tissue-resident sentinels and first responders to damage or invasion. Subsequently, we consider extracellular vesicle release during bacterial infection, how immunomodulation can avoid compromising *Mycobacterium tuberculosis* clearance, and how innate immunity jeopardises the organism during rheumatoid arthritis. Moreover, we ponder over the predictive value of cardiac troponin in influenza, the virtues of cashew nuts and bilirubin, as well as holes in the heart. Finally, we learn that mandibular movement during swallowing increases with the vertical dimension of occlusion, and that early controlled relaxation incisions restore the blood supply to the extremities in harlequin ichthyosis neonates.

Spotlight on reviews

Guards! Guards! How innate lymphoid cells ensure local law and order

It is the year 390 BC, a night illuminated by a full moon, and Ancient Rome is in dire trouble. Following a diplomatic failure,¹ the Gallic army led by Brennus has just waltzed straight onto Rome, inflicted a crushing defeat on the unprepared Roman forces and raided the city. Those who have not fled are entrenched on top of the steep and fortified Capitoline Hill, besieged by the Gauls... and these just figured out how to climb

up the cliff. Skilled, silent, and stealthy – no one notices anything. No one, but the geese.

As the sacred animal of Juno, the geese are well cared for on the Capitoline, and prove to be light sleepers who were not pleased about the visitors. Quacking and honking at full volume, they wake up the Roman soldiers, who quickly send the intruders into the afterlife.²

More than two millennia after the heroic geese incident, their equivalent in terms of immune cells has been discovered in a number of organs: innate lymphoid cells (ILCs), the latest addition to the mammalian immune system's family tree [1,2]. Unlike most members of both the innate and adaptive immune system, known to patrol

* Corresponding author. University of Copenhagen, BRIC Biotech Research & Innovation Centre, Anders Lund Group, Ole Maaløes Vej 5, 2200 Copenhagen, Denmark.

E-mail address: sophia.hafner@bric.ku.dk.

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¹ Even back then, killing ambassadors during negotiations was rather frowned upon.

² <https://www.warhistoryonline.com/ancient-history/how-holy-geese-saved-the-republic-in-390-bce-during-the-first-sack-of-rome.html>.

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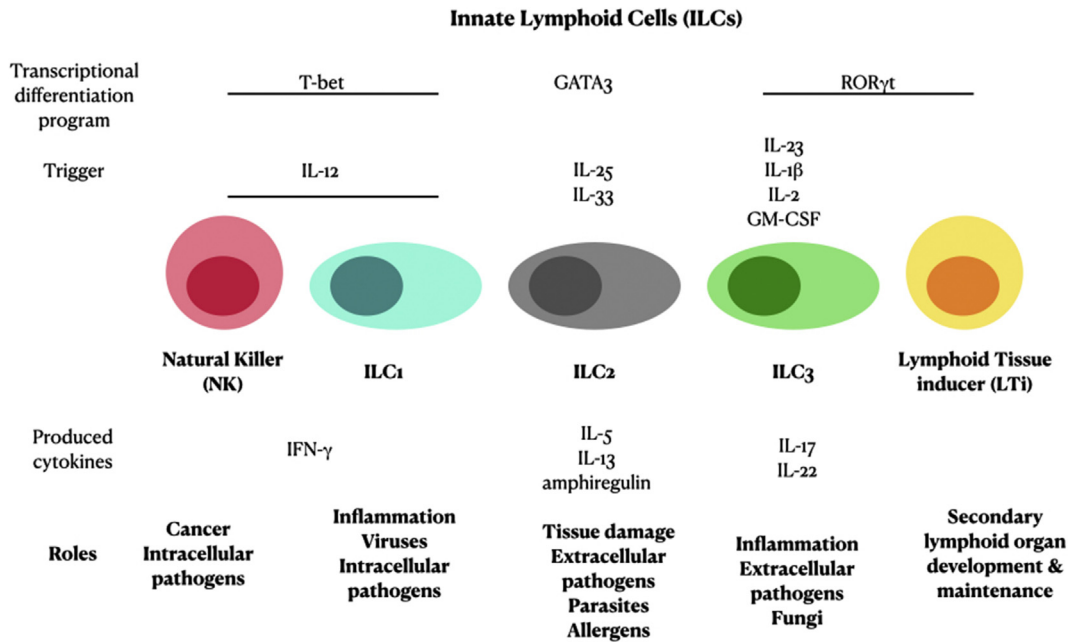


Fig. 1 Classification of Innate Lymphoid Cells (ILCs). ILCs are divided in five types, depending on the transcription factor governing their differentiation, their driver cytokines (trigger), and the cytokines they produce. Natural killer cells are mobile and cytotoxic, ILC1-3 are tissue-resident and non-cytotoxic. LTi cells are essential for secondary lymphoid organ development during embryogenesis. The main functions of the different ILC types are summarised.

the body, they are tissue-resident cells devoid of rearranged antigen-specific (RAG) receptors found mostly on mucosal barrier surfaces and thus at the front lines of host defences [3,4]. Their most prominent feature is the ability to produce a strong and immediate warning signal in the form of copious amounts of specific cytokines upon the detection of tissue injury or infection. Over the past decade, ILCs have been thoroughly investigated and shown to play crucial roles in the earliest responses to a broad panel of pathogens, damages, and tissue homeostasis maintenance [1].

As announced in the editorial by Kanellopoulos and Ojcius [5], this issue of the *Biomedical Journal* is dedicated to ILCs, and features four excellent reviews composed by experts in the field, giving emphasis to their many aspects and potentials [3,4,6,7].

All four articles comfortably acquaint any non-specialist reader with the basic ILC classification into five groups, based on fairly clear cut molecular characteristics: natural killer (NK) cells, lymphoid tissue inducer (LTi) cells, and ILC1-3s. The latter are distinguished by their developmental transcription programs, governed by T-bet, GATA3, and ROR γ t respectively, and their effector programs mirroring those of T-helper Th1, Th2, and Th17 cells.

As a result, ILC1s are triggered by interleukin (IL)-12 in order to react to tissue inflammation, viruses, and intracellular pathogens by producing IFN- γ . ILC2s in turn respond to IL-25 and IL-33 related to tissue damage, extracellular bacteria, parasites, and allergens with the secretion of IL-5, IL-13, and amphiregulin. Last but not least, ILC3s sense IL-23, IL-1 β , IL-2, and GM-CSF linked to local inflammation,

and react with the production of IL-17, IL-22, or both [2–4,6,7] [Fig. 1].

To begin the journey, Nabekura and Shibuya – experts in immunoreceptors - provide us with deeper insights specifically on ILC1s and their closest relatives, NK cells [6]. Indeed, as exemplified in the first part of the review, they share the reliance on T-bet for maturation, IL-12 as a driver cytokine, IFN- γ production, and similar cytokine receptors. However, as later elaborated notably by Blanquart et al. [4], ILC1s and NK cells arise from different precursors, and ILC1s lack both mobility and cytotoxicity [6]. Subsequently, the authors proceed to elaborate on the roles of ILC1s in specific organs. Indeed, the cells call many tissues their home, notably the liver, intestines, spleen, lymph nodes, and adipose tissue [1,2]. On this occasion, the authors ensure to remind the reader to keep in mind that most studies stem from mice, whose ILC populations display certain marked differences with humans, in particular the fact that they reside mainly in the murine liver, but are much less compartmentalised in the human organism.

Nabekura et al. focus here on the liver, intestine, and adipose tissue. In the liver, ILC1s are early responders to viral infections and pivotal to limit viral replication. In addition, they promote hepatocyte survival following drug-induced liver injury via Bcl-xL. At the level of the intestine, the cells are involved in dissemination control of bacteria and parasites, but can also play a deleterious role by amplifying mucosal inflammation during colitis [8]. This becomes even more apparent in the case of the adipose tissue, where ILC1s promote the development of an inflammatory environment and mediate insulin resistance [6].

Finally, the authors mention the probable potential for long-term ILC1 memory following viral liver infection and stress that the underlying molecular signalling pathways are yet to be elucidated [6].

Complementing this very instructive overview on the roles of ILC1s in the adult organism, Blanquart et al. and van der Pavert take us back to the origins of all ILCs [4], and LTi cells in particular [7]. All lymphoid cells arise from common lymphoid progenitors (CLPs), and the subsequent sequential activation of specific translational programs gradually restricts their differentiation potential. Further details are very well resumed in Fig. 1 by Blanquart et al. [4].

Serge van de Pavert, whose team specialises in ILC3s, dedicates his review to the detailed description of origins and fates of a very special case among ILCs, lymphoid tissue inducer (LTi) cells. LTis step into the limelight way before the other four types, as they are indispensable for the formation of secondary lymphoid organs (mesenteric and peripheral lymph nodes, Peyer's patches) during embryogenesis. With great care to describe the relevant murine models, the author guides us through the spatiotemporal course of LTi development, starting on embryonic day E8.5, when various haematopoietic progenitors bud off the endothelium and migrate to the foetal liver (FL). There, CLPs are pushed down the ILC fate by TCF-1 and ID2 signalling, turning them into α LP cells. This is where the schism occurs – cells expressing the PLZF transcription factor proceed to the ILC1/2/3, while those expressing the chemokine receptors CXCR5/6 become LTi progenitors (LTiP). CXCL13 attracts the LTiPs to form aggregates termed “lymph node (LN) anlagen” in specific locations, where they further mature into LTi₀, then LTi₄ and LTi₄-II cells through retinoic acid fuelled ROR γ t expression. LTi₄ cells eventually interact with the mesenchymal precursors of the lymphoid tissue organiser (LTo) cells, which amplifies the production of cytokines and attracts more LTiPs. The final LN organisation occurs through the differentiation of stromal cell subsets and immigration of specific lymphocytes [7].

In the adult organism, embryonic LTi cells are replaced by bone-marrow haematopoietic stem cell (HSC)-derived LTi cells and reside mainly in the lymph nodes and the gut, which also harbours an LTi-like ILC3 subpopulation. However, the role of adult LTi cells remains nebulous so far [7].

This detailed account on LTi ontology and the underlying transcriptional programs perfectly prepare the ground for further insights into ILC generation and function, this time under the aspect of one of the most conserved developmental pathways – Notch signalling. Rachel Golub's research encompasses both ILC ontogenesis and their role in hepatocarcinoma. Countless mouse models at hand, she dissects here the contribution of Notch in ILC development, function, and plasticity [3]. At first, the author provides a helpful description of the Notch pathway members and signalling cascade, the available model systems, and finally global ILC ontogeny. The latter transitions into the report on the implication of Notch signalling during the progressive ILC differentiation. In short, Notch is not required for the early ILC lineage specification until the ILC progenitor (ILCP) stage, but essential for the proliferation of ILC2 progenitors. Moreover, adult ILC3s need strong Notch signalling to

achieve final differentiation, and as the bone marrow does not provide these conditions, ILCPs circulate until they encounter Notch ligands, most likely in the small intestine. Finally, the role of Notch in balancing ILC3 subsets and thus cytokine homeostasis is explored.

The review series concludes with a daring note. Sexual disparity is a much too often ignored factor in the search for the physio(patho)logical truth, despite undeniable evidence for sex hormones meddling with most processes, including immunity [9,10]. The team of Jean-Charles Guéry has significantly advanced our understanding of sex differences in immunity [11]. Here, Blanquart et al. describe sex-correlated variations in ILC development and function in mice and speculate on their potential pathological significance [4].

After a general introduction on ILC types and sex steroid hormone signalling, the authors focus on the case of NK cells and ILC2s. NK cells display high levels of oestrogen receptor 1 (ESR1), while ILC2s carry appreciable amounts of androgen receptor (AR), rendering the hypothesis of differential regulation in males and females plausible. Indeed, female mice harbour more ILC2s and ILC2 progenitors in their lungs at steady state, concomitantly with a more responsive gene signature and higher capacities to produce IL-5 and IL-13 upon stimulation. Taking into consideration that asthma has a bias towards females and that male mice have a reduced susceptibility to allergic airway inflammation, it is tempting to conjecture that the AR exerts an inhibitory effect on ILC2 development and activity. Nevertheless, Blanquart et al. call for caution, given that these differences disappear upon allergen challenge and inflammation [4].

One common motive found in all four reviews is the abovementioned ambiguous role of ILCs in health and disease, and the obvious question how these insights could be harnessed for therapeutic strategies [5–7]. Notch signalling for instance can drive the acquisition of ILC3 features by ILC2s, repress ILC2 IFN- γ production and maybe recruit ILC3 subsets for dermis repair, altogether reasons enough to consider Notch as a means to tune ILCs in inflammation [3]. Furthermore, ILC2s could participate in airway hyperreactivity just as much as in bronchial epithelium regeneration [4], ILC1s have been involved with chronic inflammation of the gut and lungs [8], exacerbation of kidney injury and contact hypersensitivity, and adult LTis might play a role in lymph tissue repair but also the formation of tertiary lymphoid structures in cancer [7]. All these observations boil down to the conclusion that only a better understanding of the underlying molecular pathways and precise weighing of proinflammatory versus survival signals will tell the true extent of ILC implication in these processes. A challenging task – because ILCs are very dynamic, adjust to numerous niches, derive from different progenitors, and can even transit between types [7].

On the whole, these articles allow for a great overview on the state of the art of ILC-related research, as well as an appraisal of the field's complexity, which extends even further into the realms of “neuroimmunity” and cancer [1,12,13]. Without doubt, they equally foreshadow more valuable insights to come, and yield hopes for a better control of the inflammation-repair balance.

Also in this issue

Editorial

Red carpet for very important cells Kanellopoulos and Ojcius roll out the red carpet, aka editorial, for the four reviews about the many aspects of innate lymphoid cells (ILCs) at the heart of this special issue. Seamlessly complementing the spotlight on reviews section above, they concisely sum up the key findings of every study and highlight their diversity [5].

Reviews

You've got mail

Recently we were reminded of the monumental economic importance of cargo trafficking around the planet when the giant merchandise ship Ever Given got stuck in the Suez canal in March, obstructing one of the world's busiest trading routes for six days. Although the internet community quite enjoyed the show and rooted for the "Guy With A Digger At The Suez Canal" on Twitter,³ trading companies reported hundred million dollars of loss per hour.⁴

But cargo transport is not only the backbone of the modern economy, it is also fundamental for cell–cell communication, either between host cells, or dispatched and loaded with virulence factors by pathogens. Almost all cells set free extracellular vesicles (EVs) loaded with all kinds of proteins and nucleic acids [14,15].

Here, Spencer and Yeruva discuss the heterogeneity of extracellular vesicles and their role during bacterial infection [16]. The authors first provide a detailed description of the diversity of EVs in size, content, and biogenesis pathways. Notably, they emphasise that different cell types generate different types of EVs. Thereupon, they focus on EV release by cells infected by bacteria, and how this process is both part of the immune response and can be hijacked by pathogens. The review concludes with pertinent open questions regarding the impact of EVs on the inflammatory response and to which degree they benefit the host or the invader [16].

The white plague

Back in the 19th century, tuberculosis was considered a romantic affliction, where young artists were "devoured by ardour", and inspired a considerable number of works, from operas to computer games [17]. In this day and age, the disease caused by *Mycobacterium tuberculosis* has admittedly lost its charm, but not its gravity, given that a quarter of the human population carries the pathogen, and that about 10 million individuals develop tuberculosis and 1.5 million die from it per year [18]. *M. tuberculosis* strikes once the immune system is compromised, which can result from manifold causes: immunodeficiency, cancer therapy, HIV infection, or treatment of autoimmune diseases [19].

The last scenario attracted the attention of Segueni et al., who examine in the present review the potential risk of interfering with different pathways related to the innate immune system to compromise the natural defences against *M. tuberculosis* [20]. Special attention is paid to the TNF pathway, targeted in rheumatoid arthritis (RA) patients [21], and interleukin-17 (IL-17), whose inhibition benefits psoriasis patients [22].

Extensively documented by mouse models and their own studies, the authors demonstrate that muzzling of TNF, IL1- α / β , or IFN γ , but not of IL-17A/F and IL-22 disrupts the protection against *M. tuberculosis* infection [20].

Mutiny on the bones

Friend or foe – alas, the immune system can be both, and the consequences dire, once an autoimmune disease-flagged mutiny has begun. Rheumatoid arthritis (RA) for instance consists in the chronic inflammation of the joints, leading to progressive cartilage and bone degradation. Countless genetic and environmental factors contribute to this complex disease, which rigs both the innate and adaptive immune system against their organism of origin. Over the past decades, remarkable progress has been made in deciphering the risk factors and molecular contributors of RA [23].

In order to sum up the state of the art, Edilova et al. provide in their review the reader with an exhaustive description how different members of the innate immune system, such as macrophages, dendritic cells, neutrophils, and innate lymphoid cells contribute to the establishment and maintenance of the inflammatory RA microenvironment. In complement, the authors describe how these insights are and could be put to a therapeutic use by immunomodulation [24].

Taking the flu to heart

One of the first reported collateral damages to be caused by COVID-19, other than harm to the respiratory tract, was myocardial injury [25]. This did actually not come as a major surprise, because a solid connection between infections and acute coronary syndrome (ACS) had already been established nearly a century ago [26]. The underlying mechanisms are manifold, such as the direct invasion by SARS-CoV-2 of cardiomyocytes bearing the ACE-2 receptor for example, or more indirect effects, like cytokine storms [25]. In order to prevent serious damage to the myocardium in time, it is of crucial importance to monitor reliable biomarkers that could foreshadow cardiac injury.

Cardiac troponins (cTN) are generally used when cardiac injury is suspected, unrelated of infection, but Lippi and Sanchis-Gomar suggest that screening of these markers in patients with Influenza might be equally beneficial [27]. In order to test their theory, the authors carried out a literature review to investigate the correlation of cTN levels in Influenza virus patients and correlate them to the disease course. Their thorough discussion of the literature leads to the conclusion that cTN elevations are rare or self-limited in the majority of patients, but that a sudden increase paralleled with cardiovascular symptoms strongly indicates cardiac injury, thus weighting in favour of a cTN immunoassay in patients with cardiac symptoms or comorbidities [27].

³ <https://twitter.com/SuezDiggerGuy>.

⁴ <https://www.forbes.com/sites/mikeosullivan/2021/03/27/grounded-ever-given-tells-much-about-the-state-of-our-economy/?sh=2d98bd348ddf>.

Original articles

Children of men

“It is the year 2027, and humanity is at the brink of collapse and facing extinction after two decades of complete infertility”.

Of course, the situation is not as dire as in the 2006 science fiction thriller, but there are some concerns about the rather dramatic decline of human fertility worldwide over the past two centuries [28]. Semen quality has even decreased by up to 60% just over the last 40 years according to some studies [29], although fertility as a whole is without doubt a complex phenomenon with physiological and environmental, but also cultural and psychological components [28]. Attempts to counteract the trend range from the promotion of healthy life styles to medication. Clomiphene is a veteran among the latter. The selective oestrogen receptor modulator basically ushered in the era of assisted reproductive technology over half a century ago. Classically used to treat infertility in women by stimulating ovulation [30], it has also been used for the treatment of hypogonadism in men [31]. But the role of healthy nutrition is not to be underestimated either in the multi-causal matter of fertility. The attribution of stimulating powers to natural products, often with suggestive forms, is nearly as old as humanity, but some contain a grain of truth – especially if it is whole grains, officially recommended to improve fertility [32].

Akomolafe et al. suggest to make nature and medication join forces by testing clomiphene citrate, cashew nut-supplemented diet, and a combination of both on rats.

They show that the addition of cashew nuts to the food substantially potentiates the positive effect of clomiphene citrate on multiple fertility aspects, such as testosterone levels, sperm count, or antioxidant status of the reproductive organs [33], adding more good arguments to consume the tasty snack loaded in dietary minerals.

Don't eat the yellow snow

Bilirubin (BIL) is the end product of the enzymatic degradation of heme from senescent red blood cells in the spleen and responsible for the yellowish colour of bruises and jaundice [34]. For quite a long time, it was eyed rather suspiciously, as excessive BIL levels can indeed be a sign for severe liver disease, but nowadays, it is recognised as one of the most potent antioxidants in nature, and a powerful signalling molecule, notably through its ability to inhibit nearly every member of the immune system [34,35]. Nevertheless, its protective *versus* damaging effects specifically in the context of neuropathological conditions are not yet fully disentangled [34].

Here, Chan et al. conducted a retrospective study on type 2 diabetes patients with BIL levels in the normal range from the Chang Gung Memorial Hospital (Taiwan), focusing on the progression of albuminuria, a risk factor for kidney failure and cardiovascular events.

They come to the conclusion that higher serum BIL levels correlate with a decreased risk to albuminuria progression, thus confirming the protective role of BIL [36].

Heartbroken

It is almost frightening, to what degree human beings enter the world in an unfinished state. During the first months after birth, massive post-processing takes place: ossification of the fontanelles, synaptic pruning in the central nervous system, or the education of the immune system by the intestinal microbiota [37,38]. These events are evolutionarily programmed, but sometimes the organism has to mend other congenital defects, notably at the level of heart architecture.

Patent foramen ovale (PFO) and atrial septal defect (ASD) for example are holes in the separation between the two upper heart chambers, causing abnormal blood flow either from the right to the left, or left to the right chambers respectively. Ventral septal defect (VSD) refers to a hole in the wall separating the heart's two lower chambers, and patent ductus arteriosus (PDA) is a foetal blood vessel connecting the aorta and the pulmonary artery [39]. In most cases, these defects are resolved within hours to months after birth. The downstream impact of their persistence is extremely variable – up to 25% of the population have PFO without further complications but an increased risk for paradoxical thromboembolic stroke – whereas PDA leads to pulmonary hypertension and right heart failure.

Here, Yuan et al. conducted an extensive retrospective cohort study in order to establish the baseline characteristics in new-borns with PFO and/or PDA, determine the spontaneous closure rates of various heart defects, and pinpoint predictive elements for either spontaneous closure or persistence of PDA or PFO [40]. The authors discover several interesting correlations between the different conditions, such as the association of PFO with early birth age and low birth weight, and that the persistence of PFO or PDA at 12 months of age strongly correlated with complex congenital heart disease. Overall the study provides valuable material for determining cases requiring regular echocardiographic monitoring [40].

Say “Emma”

Making people go “cheese” is a rather hackneyed way to get them to smile for photos. Making them say “Emma” however is apparently a method to estimate their vertical dimension of occlusion (VDO), which corresponds in layman's terms to the distance between the frontal upper and lower jaw with a fully closed mouth and upon maximal contact by the teeth of opposing arches. For obvious reasons, the VDO plays an important role both in facial aesthetics and phonetics. Tooth decay, loss, and bruxism (teeth grinding) lead to VDO loss and impact thus both appearance and articulation. Restoring or increasing it ranks among the more delicate and expensive prosthodontic treatments, given that it requires precisely tailored crowns or implants [41].

In addition, it has to be ensured that VDO increase does not disturb other functions, such as the mandibular movement during deglutition. Therefore, Shen et al. examine in their study the relation between a gradual artificial VDO increase and mandibular movement during swallowing in healthy subjects. Indeed, they find a positive correlation between VDO and mandibular movement in the lateral direction, but also point out that natural physical adaptation is likely to temper most initial discomfort [42].

Brief communication

Survival on a knife's edge

Arlecchino, or the Harlequin, is a comic stock character from the Italian commedia dell'arte, characterised by a mischievous character and a strong leaning towards acrobatics. Although named in reference to his chequered costume, harlequin ichthyosis (HI) could not be further away from amusement, as it refers to an exceedingly rare disorder linked to mutations of the keratinocyte lipid transporter gene *ABCA12*, causing severe hyperkeratosis [43].

In lieu of normal skin, patients are born with hard, fissured plaques and constriction bands that strangulate the trunk and the limbs. These rapidly lead to respiratory difficulties and cutting off the blood supply to the extremities, potentially causing their necrosis and autoamputation. For centuries, HI was a death sentence a few days after birth, however improved neonatal intensive care, the use of retinoids, and the permanent management of moisture, temperature, and infections have allowed a handful of patients to reach adulthood [44].

Moreover, the damage exerted by the constrictive bands can be averted by performing controlled relaxation incisions, similar to escharotomies used to treat full-thickness burns. In this brief communication, Chu et al. describe the successful resolution of compartment syndrome and salvaging of all digits in a preterm new-born suffering from HI thanks to an early and extensive pressure relief by incision [45].

Disclaimer

The title is meant to be an obvious tribute to the homonymous novel by Terry Prattchet.

Conflicts of interest

The author declares no conflicts of interest.

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