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## Highlights

# The two faces of invariant natural killer T cells



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### ABSTRACT

In this issue of the *Biomedical Journal*, we take a look at some of the immune system's most peculiar cells, invariant natural killer T cells, which have features of both innate and adaptive cells. We also highlight a clinical study revealing that high serum phosphate levels could show that it's time to start dialysis in patients with chronic kidney diseases. Finally, this issue also includes some case reports, including an unusual case of aspergillosis related to long-term inhaler use.

## Spotlight on reviews

### The two faces of invariant natural killer T cells

The theoretical fence between what constitutes innate immunity and what constitutes adaptive immunity was erected many decades ago. Yet once in a while, there comes a challenger that defies classification. This issue of the *Biomedical Journal* includes two reviews describing invariant natural killer T cells (iNKTs), T cell receptor-expressing cells with an emerging role in many human diseases that have been baffling researchers with their innate-like features.

In their review, Birkholz and Kronenberg [1] describe some of the properties and antigens of these curious cells. A hybrid by nature, iNKT cells express both markers of innate natural killer (NK) cells, such as CD161, and a  $\alpha\beta$  T cell receptor (TCR) with some unusual properties [Fig. 1]. Unlike conventional T cells that recognize peptides bound to highly polymorphic major histocompatibility complex (MHC) class I and II molecules, the TCR of iNKT cells recognizes lipid antigens bound to

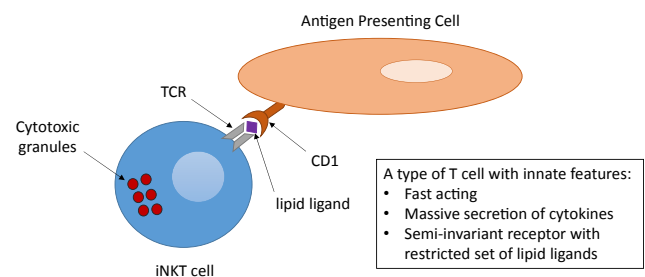


Fig. 1 – Despite the fact that they express a T cell receptor, invariant Natural Killer T (iNKT) cells have several properties typical of cells of the innate immune system.

a the poorly-polymorphic CD1d molecule. All in all, this combination of traits gives rise to a cell capable of rapidly secreting copious amounts of cytokines and cytotoxic granules in response to the activation of its TCR by a specific self or foreign lipid ligand [2].

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iNKT cells recognize lipids from microbes, tumors and allergens and play a role in many diseases [3–5]. Tard et al. [6] describe how our understanding of the role of these cells in diabetes has progressed ever since the early finding of reduced iNKT cells numbers in diabetic (type I) NOD mice [7]. Functional experiments soon followed, with the demonstration that the transfer of iNKT cells to NOD mice protected them from developing diabetes [8], while a similar protective effect was brought about by the injection of the iNKT cell-stimulating lipid,  $\alpha$ -galactosylceramide ( $\alpha$ -GalCer) [9]. This protection is thought to be mediated in part through IL-4, which is abundantly secreted by iNKT cells following their stimulation and prevents the onset of diabetes [10]. In addition, iNKT cells inhibit the differentiation of autoreactive T cells responsible for the destruction of pancreatic  $\beta$ -cells [11].

Despite these clear findings in mice, human studies of iNKT cells in type I diabetes have yielded inconsistent results, with studies reporting similar, high or low frequencies of iNKT cells in diabetic patients. This may be because iNKT numbers vary greatly from person to person (ranging from 0.01% up to nearly 1% of peripheral lymphocytes) [2]. Nonetheless, this has not precluded the testing of iNKT-stimulating therapies, with studies underway to develop optimized  $\alpha$ -GalCer analogs [12]. Such therapies could also be relevant for patients with type II diabetes, in light of growing evidence that these glycolipid-recognizing cells play a role in obesity-related inflammation and insulin resistance [13].

iNKT cells may well have earned a reputation as the duck-billed platypus of the immune system, but despite their confusing appearance, one thing remains clear: their widespread role in human diseases, from diabetes, allergies to cancer is being uncovered, and we can expect therapies manipulating this intriguing cell subset in years to come.

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## Spotlight on original articles

### *Deciding on dialysis: serum phosphate as a biomarker in chronic kidney disease*

Our expanding waistlines coupled with increasing life expectancy has meant that the prevalence of the chronic kidney disease (CKD) is on the rise [14]. In the absence of an appropriate kidney donor, the only treatment for people with advanced CKD is dialysis. Yet, determining when exactly to initiate dialysis is often a complicated decision that varies from one treatment center to the next. In this issue of the *Biomedical Journal*, Lu and colleagues [15] identify high serum phosphate levels as clinical marker for the initiation of dialysis.

CKD is a condition characterized by gradual loss of kidney function over time and affects a staggering 8–16% of people worldwide [16]. If left untreated, patients may develop life-threatening complications including pulmonary edema, cardiovascular disease and extreme hyperkalemia. Renal replacement therapy, and notably hemodialysis, is a last resort in the advanced stages of disease, but is costly, and renders patients dependent on highly frequent hospital visits lasting several hours. Previous guidelines relied heavily on glomerular filtration rate (GFR; the rate of blood filtered by the kidneys) as a

marker indicating the need for dialysis [17], but several studies have since shown that starting patients on dialysis at the cut-off GFR may in fact be harmful in many cases [18,19]. Recent guidelines offer more room for physician's to use their own clinical judgement [20]; however, objective laboratory variables are needed to facilitate this decision.

Lu et al. retrospectively analyzed the medical records of all patients with advanced stage CKD attending a Taiwanese tertiary medical center over a four year period and collected data on demographics, comorbidities, underlying diseases, duration of nephrology care, use of phosphate binders, and laboratory findings. They divided patients into two groups: a dialysis-initiated ( $n = 209$ ) and non-dialysis ( $n = 83$ ) group and evaluated potential risk factors associated with the initiation of dialysis using logistic regression models. Besides conventional laboratory markers (urea and serum creatinine levels), serum phosphate levels were significantly associated with the initiation of dialysis after adjusting for other factors, with a 110% increased risk of initiation for each 1 mg/dL increase of serum phosphate. Moreover, serum phosphate was the only tested variable that was within the normal range in the control group, but very high in the dialysis-initiated group.

It has long been known that high serum phosphate is a common problem in patients with CKD and may lead to mineral bone diseases, vascular calcification and cardiovascular disease [21], yet its prognostic value is underappreciated. If replicated in a larger prospective cohort, phosphate levels may prove to be a powerful biomarker, especially in patients with complex uremic syndrome, and may help physicians to make the difficult decision of whether or not to initiate dialysis.

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## Also in this issue:

### Review articles

#### *Studying the link between drugs and food in flies*

In this review, Landayan and Wolf [22] discuss the use of *Drosophila* as a model organism to study overlap in the neural circuitry controlling the reward sensation associated with food and drugs.

#### *The challenges of amblyopia treatment*

Amblyopia or 'lazy eye' occurs if visual signals are not processed correctly in the brain, leading to impaired vision that cannot be corrected by glasses or contact lenses. It has proven to be a difficult condition to manage, as described by Maco-nachie and Gottlob in this review [23], where they discuss some of the challenges and future directions in treatment.

### Original articles

#### *Top marks for thyroid nodule malignancy scoring system*

Most lumps (or nodules) that appear in the thyroid are harmless. Risk of malignancy is assessed by fine-needle aspiration cytology (FNAC), yet until a few years ago, there existed no standard way to interpret the results of this test. In this retrospective analysis of 392 FNACs, Arul et al. [24] validate the recently developed Bethesda system for reporting thyroid cytopathology [25] as an accurate scoring system for

predicting malignancy and identifying patients requiring further treatment.

#### High osteonectin levels signal danger for chronic heart failure patients

The collagen-binding protein osteonectin (OSN) controls extracellular matrix remodeling after myocardial infarction (MI) [26], but its role in chronic heart failure (CHF) is unclear. Berezin and Kremer [27] investigate the prognostic value of OSN in 154 patients with ischemic symptomatic CHF and surprisingly report that high circulating levels of OSN are associated with an increased risk of CHF-related death or readmission.

#### Bigger is not always better in hip transplants

Advancements in the materials used in hip transplants have enabled the size of prosthetic femoral head to be increased without increasing wear. However, it is still unclear whether a large head (>36 mm) may decrease the dislocation rate and improve hip range of motion. In this retrospective study of 95 patients undergoing ceramic-on-ceramic total hip arthroplasty, Lu and colleagues [28] find that functional outcome and early complications are similar between large and small femoral heads.

#### Determining the best methods to train the next generation of doctors

Postgraduate programs that offer general medical training were first rolled out in Taiwan in 2003, and are thought to improve patient care, clinical skills and doctor-patient communication. Hsu and colleagues [29] use an objective structured clinical examination to assess learning through different training programs and find that a 6 month training program prepares young doctors for clinical practice just as well as a 1 year training program.

#### Brief communication

##### Rare case of aspergillosis evading a healthy immune system

In this case report, Saha et al. [30] describe a curious case of laryngeal aspergillosis occurring in an immunocompetent asthmatic individual, likely linked to long-term inhalational steroid use.

#### Correspondence

##### A peculiar case of muscular dystrophy

Ahmad and Kumar [31] report a case of adult onset myotonic muscular dystrophy type I in a soldier with several unusual features, including the lack of affected family members or systemic features and marked atrophy of the tongue.

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