Highlights

The two faces of invariant natural killer T cells

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ARTICLE INFO

Article history:
Available online 9 March 2016

Keywords:
Invariant natural killer cells
Diabetes
Chronic kidney disease
Dialysis

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 semi-invariant 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 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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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.
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, α-galactosylceramide (α-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 β-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 cell 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 α-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.

**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 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 α-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].

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.

**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 Macnachie 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
High osteonection 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.

References
[1] Birkholz AM, Kronenberg M. Antigen specificity of invariant natural killer T-cells. Biomed J 2015;38:470–83.
[2] Bendelac A, Savage PB, Teyton L. The biology of NKT cells. Annu Rev Immunol 2007;25:297–336.
[3] Godo M, Sessler T, Hamar P. Role of invariant natural killer T (iNKT) cells in systemic lupus erythematosus. Curr Med Chem 2008;15:1778–87.
[4] Vivier E, Ugolini S, Blaise D, Chabannon C, Brossay L. Targeting natural killer cells and natural killer T cells in cancer. Nat Rev Immunol 2012;12:239–52.
[5] Thomas SY, Lilly CM, Luster AD. Invariant natural killer T cells in bronchial asthma. N Engl J Med 2006;354:2616–6.
[6] Tard C, Rouxel O, Lehuen A. Regulatory role of natural killer T cells in diabetes. Biomed J 2015;38:484–95.
[7] Gombert JM, Herbelin A, Tancrède-Bohin E, Dy M, Carnaud C, Bach JF. Early quantitative and functional deficiency of NK1.1–like thymocytes in the NOD mouse. Eur J Immunol 1996;26:2989–98.
[8] Lehuen A, Lantz O, Beaudoin L, Laloux V, Carnaud C, Bendelac A, et al. Overexpression of natural killer T cells protects Valpha14–Jalpha281 transgenic nonobese diabetic mice against diabetes. J Exp Med 1998;188:1831–9.
[9] Wang B, Geng YB, Wang CR. CD1-restricted NK T cells protect nonobese diabetic mice from developing diabetes. J Exp Med 2001;194:313–20.
[10] Rapoport MJ, Jaramillo A, Zipris D, Lazarus AH, Serreze DV, Leiter EH, et al. Interleukin-4 reverses T cell proliferative unresponsiveness and prevents the onset of diabetes in nonobese diabetic mice. J Exp Med 1993;178:87–99.
[11] Beaudoin I, Laloux V, Novak J, Lucas B, Lehuen A. NKT cells inhibit the onset of diabetes by impairing the development of pathogenic T cells specific for pancreatic beta cells. Immunity 2002;17:725–36.
[12] Blumenfeld HJ, Tohn R, Haeryfar SM, Liu Y, Savage PB, Delovitch TL. Structure-guided design of an invariant natural killer T cell agonist for optimum protection from type 1 diabetes in non-obese diabetic mice. Clin Exp Immunol 2011;166:121–33.
[13] Schipper HS, Rahkshandehroo M, van de Graaf SFJ, Venken K, Koppen A, Sienstra R, et al. Natural killer T cells in adipose tissue prevent insulin resistance. J Clin Invest 2012;122:3343–54.
[14] Reutens AT, Atkins R. Epidemiology of diabetic nephropathy. Contrib Nephrol 2011;170:1–7.
[15] Lu YA, Lee SY, Lin HY, Liu YC, Kao HK, Chen YC, et al. Serum phosphate as an additional marker for initiating hemodialysis in patients with advanced chronic kidney disease. Biomed J 2015;38:531–7.
[16] Jha V, Garcia-Garcia G, Iseki K, Li Z, Naucker S, Yang CW, et al. Chronic kidney disease: global dimension and perspectives. Lancet 2013;382(9888):260–72.
[17] National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1–266.
[18] Rosansky SJ, Cencarini G, Clark WF, Eggers P, Germaine M, Glassock R, et al. Dialysis initiation: what’s the rush? Semin Dial 2013;26:650–7.
[19] Rosansky SJ, Eggers P, Jackson K, Glassock R, Clark WF. Early start of hemodialysis may be harmful. Arch Intern Med 2011;171:396–403.
[20] Group, KDIGO/KCW. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1–150.
[21] Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 2005;16:520–8.
[22] Landayan D, Wolf FW. Shared neurocircuitry underlying feeding and drugs of abuse in Drosophila. Biomed J 2015;38:496–509.
[23] Maconachie GD, Gottlob I. The challenges of amblyopia treatment. Biomed J 2015;38:510–6.
[24] Arul P, Akshatha C, Masilamani S. A study of malignancy rates in different diagnostic categories of the Bethesda system for reporting thyroid cytopathology: an institutional experience. Biomed J 2015;38:517–22.

[25] Cibas ES, Ali SZ. NCI Thyroid FNA State of the Science Conference. The Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol 2009;132:658–65.

[26] McCurdy SM, Dai Q, Zhang J, Zamilpa R, Ramirez TA, Dayah T, et al. SPARC mediates early extracellular matrix remodeling following myocardial infarction. Am J Physiol Heart Circ Physiol 2011;301:H497–505.

[27] Berezin AE, Kremzer AA. Predictive value of circulating osteonectin in patients with ischemic symptomatic chronic heart failure. Biomed J 2015;38:523–30.

[28] Lu YD, Yen SH, Kuo FC, Wang JW, Wang CJ. No benefit on functional outcomes and dislocation rates by increasing head size to 36 mm in ceramic-on-ceramic total hip arthroplasty. Biomed J 2015;38:538–43.

[29] Hsu PW, Hsieh MJ, Fu RH, Huang JL, Liao MC, Lee ST. Comparing the outcomes of different postgraduate year training programs in Taiwan. Biomed J 2015;38:544–9.

[30] Saha A, Saha K, Chatterjee U. Primary aspergillosis of vocal cord: Long-term inhalational steroid use can be the miscreant. Biomed J 2015;38:550–3.

[31] Ahmad FMH, Kumar KVS. A trigger-happy soldier with bilateral ptosis and dysphagia. Biomed J 2015;38:554–5.