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Highlights

Make immunological peace not war: Potential applications of tolerogenic dendritic cells

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ABSTRACT

In this issue of the *Biomedical Journal*, we explore the powerful immunosuppressive properties of tolerogenic dendritic cells and discuss their potential to bring about lifelong tolerance in transplantation and autoimmune disease. We also highlight an exciting new development in the field of malaria diagnosis that could facilitate early detection of the disease.

Spotlight on review

Make immunological peace not war: potential applications of tolerogenic dendritic cells

Since their discovery over 40 years ago, dendritic cells (DCs) have been widely recognized for their role in the body's surveillance system, roaming the lymphatic system and peripheral tissues searching for any sign of invasion against which to mount an immune response. But there are various sides to these professional antigen-presenting cells, which under the right conditions, contribute to making peace through immunological tolerance instead of war. In this issue of the *Biomedical Journal*, Horton et al. [1] describe the mechanisms of these tolerogenic DCs (tol-DCs) and reflect on how we might one day soon be able to harness their power to bring about lifelong immunological tolerance in transplant recipients and those suffering from autoimmune diseases.

In contrast to their immunogenic mature counterparts, immature DCs are largely tolerogenic. These so-called tol-DCs constantly migrate throughout the periphery and lymphatic system picking up innocuous self and non-self antigens, which they present to naïve T lymphocytes in the absence of co-stimulatory molecules. Besides denying T cells with the factors needed for their activation, tol-DCs limit T cell responses through several other mechanisms [Fig. 1]. Tol-DCs induce T cell anergy by binding to the CTLA-4 receptor on activated T cells [2] and actively remove potentially autoreactive T cells by inducing T cell apoptosis in a Fas-dependent manner [3]. Tol-DCs can also polarize T cells towards an immunosuppressive, regulatory phenotype [4]. Thus, these "peacekeeping" cells have become very attractive candidates for cell-based immunotherapies.

Take for example organ transplantation. Those receiving an allogeneic tissue transplant must also receive powerful immunosuppressive drugs to prevent graft rejection. However the long-term use of these drugs predisposes the cancer and opportunistic infections. Although ironically DCs are the main cause of graft rejection, tol-DCs manipulated *ex vivo* could be the solution to preventing rejection. Theoretically, recipient DCs could be isolated and loaded with donor antigen and in an environment that promotes a tolerogenic phenotype. When re-administered to the transplant recipient, the cells could

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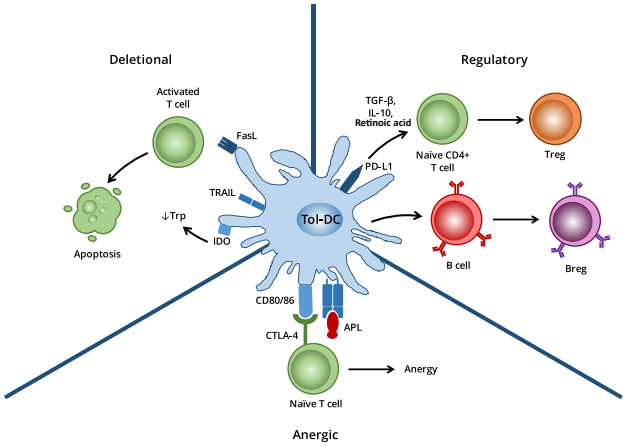

Fig. 1 How tol-DCs attenuate T lymphocyte responses. Tol-DCs inhibit T cell responses through several mechanisms: by inducing T cell anergy, by actively promoting the deletion of autoreactive cells and by promoting the polarization of naïve T cells to regulatory T cells. Figure kindly provided by Horton et al. [1].

induce tolerance to donor antigens in T lymphocytes, and potentially even lead to lifelong tolerance.

In the transplantation setting at least, the use of such an approach is still far from reality. The highly inflammatory environment of the graft poses big challenges to maintaining a stable tol-DC phenotype as the engulfment of necrotic or stressed cells cause DCs to mature into immunogenic cells [5]. As such, the introduction of unstable tol-DCs could actually increase the immune responses against the graft. An area of application that has seen more developments is the field of autoimmunity. Tol-DCs have been widely tested in animal studies of several autoimmune diseases, including arthritis [6], multiple sclerosis [7] and inflammatory bowel disease [8] and several clinical trials have shown promising findings in humans. For example, "Rheumavax" therapy, which consists of autologous DCs rendered tolerogeneic through NF-κβ inhibitor and loaded with citrullinated peptide antigens found in most rheumatoid arthritis patients, was well tolerated and increased the proportion of T regulatory cells [9].

In addition to these exciting developments, new technologies may offer the opportunity to overcome some of the current hurdles in pre-clinical work with tol-DCs. Indeed, CRISPR-Cas9 modification could make the phenotype of these cells more stable and induced pluripotent stem cells could provide ideal source cells from which to derive tol-DCs. Thus, the near future will hopefully see the development of "negative cellular vaccines", promoting immunological peace in under the foreign invasion of the transplantation setting and in the civil conflicts of autoimmunity.

Spotlight on original articles

New method for early malaria diagnosis

In 2015, there were 212 million cases of malaria and nearly 500,000 deaths due to the disease [10]. Early diagnosis and treatment is crucial to limiting deaths related to malaria and its transmission. In this issue of the *Biomedical Journal*, Paul et al. [11] report a new method for diagnosing malaria that may be able to detect infection in its very earliest stages.

Malaria is caused by *Plasmodium* parasites that are spread through the bite of infected mosquitoes. The disease manifests as acute febrile illness, and its initial symptoms can be difficult to recognize as malaria. Existing diagnostic tests rely on the visual identification (microscopy) of parasites or the detection of parasite antigens (rapid diagnostic testing) in the blood. However these tests may fail to detect infections when parasite number is low [12].

Once inside the blood, the parasite invades red blood cells, making them stiff and rigid and hence impairing circulation. The new method reported by Paul et al. exploits this property to determine whether a red blood cell (RBC) or a neighboring cell has fallen victim to *Plasmodium* infection. Using optical tweezers to trap individual RBCs with highly focused laser beams, the authors previously studied the mechanical properties of RBCs and noted that cultures of RBCs infected with *Plasmodium falciparum* showed a higher spectrum of Brownian fluctuations than non-infected cells, due to the increased rigidity of infected cells [13]. Remarkably, this change in properties did not depend on the actual presence of the parasite within cells, indicating a "bystander effect" in which hosting cells are able to influence surrounding non-hosting cells, likely through the release of ATP or cAMP [14].

Now, Paul et al. test their method in blood samples drawn from two patients infected with *Plasmodium falciparum* and four patients infected with *Plasmodium vivax*, the two species that pose the greatest threat to human health. For each sample, 25 independent measurements were taken. For RBCs infected with *P. falciparum* or *P. vivax*, the corner frequency was centered around 29 Hz, which is significantly higher than the corner frequency (25 Hz) of control RBCs. Importantly, their findings seem to confirm the bystander effect because the RBCs were chosen at random and it is likely that most of those tested were non-hosting. In addition, *P. vivax* infects mainly reticulocytes whereas the cells selected for study were mature RBCs.

These findings could constitute a promising advance in malaria diagnostics. In contrast with microscopy-based identification of the parasite on blood smears, the method is easily automated and does not require trained personnel. Perhaps the most exciting development however is that it may work during the very earliest stages of infection when parasite counts are very low, because it takes advantage of the bystander effect and does not require the analyzed RBCs to be infected. Further studies will tell whether this approach, or others based on it, could help patients to get the early, vital treatment that they need.

Also in this issue:

Original articles

Neurotransmitters boost stem cells to treat spinal cord injury
Stem cell-based treatments for spinal cord injury (SCI) is a rapidly evolving field and various cell types and cocktails of supplements have been tried and tested with varying

degrees of success [15]. In an animal study of SCI, Paulose et al. [16] report here promising results with autologous bone marrow supplemented with neurotransmitters and the neurotransmitter-stimulating agent, citicoline. This treatment reversed injury-induced reduction in the abundance of muscarinic acetylcholine receptors, which control locomoter activity. The next 'step' will be to see if these micromolecular changes translate into functional ones.

Advanced technique to image cutaneous blood flow non-invasively

Non-invasiveness techniques capable of imaging local blood flow in specified locations of the skin have important clinical applications, for example to monitor vascular occlusion in skin flaps during reconstructive surgery. However, no non-invasive techniques with high spatial resolution are currently available in clinical practice. In this animal study of laser-induced injury, Chang et al. [17] show that optical doppler tomography may be able to fill this need by providing high resolution images of blood flow at discrete user-specified locations.

The demographics of motorcycle accidents in Taiwan

In two papers, Hseih et al. report the results of their large, retrospective study investigating sex and age-related differences in motorcycle-related injuries in Taiwan. Notably, they report that women were more likely than men to wear helmets, which could explain why women sustained fewer severe injuries to the head and neck [18]. Elderly patients with motorcycle-related injuries were in fact significantly less likely than younger motorcycle users to wear and helmet [19]. Given this finding, and the poor outcome in this age group, more needs to be done to ensure the use of protective equipment.

Conflicts of interest

The author declares that there are no conflicts of interest.

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