Nanobiologics

Iqbal, Asif J

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Biographical Sketch

Dr Asif Iqbal is a Birmingham Fellow in the Institute of Cardiovascular Sciences, College of Medical and Dental Sciences, University of Birmingham. He has been studying the role of inflammation in cardiovascular disease and how we can harness endogenous mediators to regulate this process. Inflammation has been the central theme throughout his research, with particular emphasis on the anti-inflammatory mechanisms at play in both acute and chronic immune models of inflammation. His doctoral training focused on the galectins and their role in regulating leukocyte trafficking and activation of immune cells. His post-doctoral research was centred on the role chemokines play in monocyte and macrophage recruitment in the context of atherosclerosis. Following his award of a Birmingham fellowship, he now aims to bring these themes together; to investigate the actions of the galectins in pre-clinical models of vascular inflammation and atherosclerosis, and the mechanisms by which they regulate monocyte recruitment and function.

Nanobiologics- a real game changer for targeted immunotherapy

Asif J Iqbal, PhD

Institute of Cardiovascular Sciences (ICVS), College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, United Kingdom

Telephone: +441214144043

Email: a.j.iqbal@bham.ac.uk

Commentary on "Inhibiting inflammation with Myeloid cell-specific nanobiologics promotes organ transplant acceptance" by Braza *et al*, Immunity 2018

Organ transplantation has proven to be very effective in a variety of end stage diseases. Immunosuppressive agents prescribed to patients modestly improves graft survival but long term use can have detrimental side effects, leaving patients with increased risk of infection, cancer, and metabolic toxicity[1]. Strategies targeting adaptive immune cell tolerance induction have proven promising[2], however long term graft survival rates still remain sub-optimal. More recently innate immune cells, including macrophages, NK cells and monocytes have been identified as key players in the initiation of allograft rejection[3, 4]. The mechanisms by which macrophages mediate graft loss remain poorly understood.

Recently, a study by Braza *et al.,*[5] identified a macrophage activation pathway linked to allograft rejection. The authors utilised a novel myeloid-specific nanoimmunotherapy to target graft infiltrating macrophages to promote long term organ transplant acceptance. Pro-inflammatory activation of macrophages by danger associated molecular patterns (DAMPs) vimentin and high mobility group box 1 (HMGB1) by dectin-1 and TLR4 activation has been previously shown[6, 7]. Using an experimental heart transplantation mouse model, Braza *et al.,* found both vimentin and HMGB1 were upregulated in allograft infiltrating macrophages; raising the question whether these targets could promote "trained immunity". Innate immune cells can acquire trained immunity or "innate immune memory", whereby secondary non-specific challenge, after pre-exposure to certain inflammatory stimuli triggers epigenetic and metabolic changes, enhancing pro-inflammatory responses[8]. Monocytes pre-exposed to vimentin, followed by re-stimulation with HMGB1, increased pro-inflammatory IL-6 and TNFα production *in vitro*. Graft-infiltrating macrophages from dectin-1 and TLR4 deficient mouse heart allografts produced significantly lower levels of IL-6 and TNFα following *ex-vivo* stimulation.

To target trained macrophages therapeutically, Braza *et al.,* utilised myeloid specific high-density lipoproteins (HDL) nanobiologics[9]. The authors armed their nanobiologics with rapamycin, an mTOR inhibitor (termed mTORi-HDL), which has been shown to inhibit myeloid cell activation and pro-inflammatory cytokine production[10]. Heart allografts in recipient mice were shown to accumulate mTORi-HDL and its uptake preferentially by myeloid cells, namely macrophages. A treatment regime of three intravenous doses of mTORi-HDL was sufficient to prolong graft survival, compared to placebo control or mice treated with oral rapamycin. Following *ex vivo* stimulation it was shown that these macrophages had a marked reduction in pro-inflammatory cytokine production, suggesting trained macrophage responses were impaired because of mTORi-HDL treatment. Recipient allografts, blood and spleen were shown to have increased numbers of $Ly6C^{Lo}$ macrophages, reported to have anti-inflammatory properties. The authors confirmed that $Ly6C^{Lo}$ macrophages inhibited T cell proliferation and promoted regulatory T cell (Treg) expansion *in vitro*, in addition, mTORi-HDL allografts were shown to have significantly elevated Tregs counts. Irrespective of mTORi-HDL treatment, $Ly6C^{Lo}$ macrophage depletion prior to transplantation resulted in early graft rejection. Allograft survival was restored following adoptive transfer of wild-type monocytes, reinforcing the view that the mTORi-HDL therapy requires $Ly6C^{Lo}$ regulatory macrophages for successful organ transplant acceptance. Finally, the authors evaluated the impact of combinational therapy with mTORi-HDL and a CD40-CD40L targeting nanbiologic, TRAF6i-HDL[11]. They found that short-term combination therapy with mTORi-HDL/ TRAF6i-HDL synergistically promoted long-term allograft survival, and significantly outperformed either monotherapy.

The study by Braza *et al.*, clearly highlights the importance of innate immune signalling in driving trained immunity and excessive inflammation. Taking atherosclerosis as an example, Bekkering *et al.,*[12] found that exposing monocytes to a low concentration of oxLDL drove a trained proatherogenic macrophage phenotype characterised by increased pro-inflammatory cytokine production and foam cell formation. A review by Zhang and colleagues[13] emphasised the importance of trained macrophage activation pathways in pathological conditions such as cardiac remodelling and ischaemic heart disease. A recent review by Kusters and colleagues[14] reiterated the importance of immune checkpoint molecules and their potential as therapeutic targets in atherosclerosis. The concept of targeting immune checkpoint molecules, such as CD40-CD40L, as chosen by Braza *et al.,* or others, like CD80/86-CD28, is not a novel concept in of itself. However, the use of nanobiologics to successfully administer high local doses of immunosuppressive agents while limiting systemic toxicity proves to be a very attractive modality of treatment and could very well

breathe life into current treatment regimens and combinatorial therapies in the treatment of multiple chronic inflammatory diseases.

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