Harnessing B cells in immunotherapy

“...the functions of B cells that might determine the direction and impact of innate, cellular and humoral immunity in infection, cancer and transplantation.”

First draft submitted: 28 November 2015; Accepted for publication: 3 December 2015; Published online: 10 February 2016

Keywords: accommodation • antibody • B cell • complement • cytotoxicity • immunotherapy • ischemia • TACI • T cell • transplant

B cells and their progeny contribute in manifold ways to adaptive and innate immune responses. Besides producing antibodies that direct activated products of the complement cascade and phagocytes to specific targets, B cells are increasingly understood to orchestrate the development and integrate the functions of innate and adaptive immunity (see [1] for review). Here, we discuss some of the functions of B cells that might determine the direction and impact of innate, cellular and humoral immunity in infection, cancer and transplantation.

In the late 1980s, we observed that kidney transplants incompatible for ABO blood groups, and which should have suffered rapid and aggressive rejection owing to the binding of anti-blood group antibodies to the graft instead, often functioned normally if the offending antibodies were temporarily depleted and allowed to return [2]. We called this condition ‘accommodation’ to denote the apparent change in the transplanted organ that rendered it less susceptible to antibody-mediated rejection [3]. Since then, accommodation or a condition quite like it has been observed not only in transplants but also in tumors, infection, injury and inflammation [4]. Clearly, if one wishes to marshal immunity and inflammation toward the destruction of a tumor or cells harboring a latent virus, one should consider

how to prevent or reverse accommodation as it may occur. On the other hand, if one wants to selectively target an infectious agent or preserve the integrity of a transplant or injured tissue, one should consider how best to elicit accommodation. If these objectives seem obvious, approaches that safely and reliably suppress or induce accommodation are anything but obvious.

Exposure of cells, tissues and organs to subtoxic amounts of complement, cytokines, ischemia, physical injury, irradiation, microbial toxins, etc. induces resistance to lethal amounts of the same and sometimes other noxious agonists [5]. Among the most thoroughly investigated examples of such ‘accommodation’ is ischemic preconditioning [6,7]. Pre-exposure of organs or tissues to subtoxic ischemia or putative agonists of ischemic injury can reduce the severity of or even prevent severe injury when ischemia of greater severity is inflicted in the laboratory. Yet, putting this concept to clinical use has proven challenging, at least in part because one cannot know *a priori* how much ischemia or agents of ischemic injury such as intracellular Ca^{++} are needed to induce protection and how much will instead induce a level of injury to which the subsequent ischemic insult will add. For this reason, we have been keen to see if accommodation can be deliberately induced to avoid injury in transplants

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and suppressed to make tumors more susceptible to immunotherapy, chemotherapy or irradiation.

We believe that B cells might offer a system for discovery of mechanisms of accommodation pertinent to tumors and transplants. B cells are exposed to ‘genetic stress’ during recombination of immunoglobulin variable and constant regions and during somatic hypermutation. A fuller understanding of how B cells survive these events might offer clues to mechanisms that could be attacked in tumors. B cells are also exposed to environmental challenges, including bacterial products in the gut and splanchnic circulation and to hypoxia in lymphoid tissues. These conditions potentially model challenges confronted by tumors and transplants. B cells thus struggle, quite successfully, to survive these assaults [8,9]. We hope that understanding how B cells so reliably and ‘safely’ resist genotoxicity and hypoxia will provide clues about how similar responses can be generated in transplants and injured tissues and suppressed in tumors.

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Because the preponderance of antibodies and complement reside in the blood and not in extravascular spaces, antibodies appear to have the most profound impact on organ transplants, leukemias and blood-borne microorganisms and much less or no impact on transplants, tumors and microorganisms residing outside of blood vessels [10]. In fact, paradoxically, B cells and antibodies sometimes appear to inhibit effector responses, especially extravascular targets. In some cases, the ‘protective’ impact of antibodies simply reflects a correlation with the functions of regulatory B cells, the properties of which have been reviewed in detail elsewhere [11]. However, there are three other ways that antibodies might directly protect immune targets. First, antibodies that diffuse into extravascular spaces might induce accommodation rather than cytotoxicity because after antibody binds, the low, sublytic concentrations of complement in those spaces induce resistance to cytotoxicity [12]. Second, B cells and their products, including antibodies, can directly nurture tumor growth [13] and tumor-specific antibodies might bind to cellular antigens blocking cellular immune responses [14]. Small amounts of complement activated in the vicinity of tumors likewise can exert a trophic effect [15]. The ability of B cells and their products to protect tumors (and transplants) and promote growth is called ‘enhancement’. Enhancement of tumor transplants was once a subject of intense interest, and we think renewed inquiry, focused especially on prevent-

ing immune therapeutics from enhancing tumors or infected cells, might increase efficacy. Third, some antibodies, especially certain natural antibodies, can have a direct, protective or reparative impact on cellular targets [16]. How these antibodies, some encoded by germline immunoglobulin variable regions, change the biological responses of cellular targets is poorly understood but one can envision advancing immunotherapies by providing these antibodies in some setting and inhibiting their binding in others.

Two other facets of B-cell responses that might determine whether or not protective immunity or accommodation ensues are the kinetics and the breadth of the response. We glimpsed the potential importance of the kinetics of the B-cell responses in some counter-intuitive observations in mice. To explore the involvement of transmembrane activator and calcium-modulating cyclophilin ligand interactor, or TACI, in host defense we compared the ability of TACI-deficient and wild-type to clear *Citrobacter rodentium* from the gut. We had previously found that TACI promotes B-cell maturation [8,17] and that deficiency of TACI in mice and humans is associated with low-immunoglobulin levels in blood and the common variable immunodeficiency syndrome. Since clearance of *C. rodentium* depends absolutely on B-cell responses, we expected that mice lacking TACI, like immunodeficient mice, would succumb to infection. However, instead we found that while TACI-deficient mice, despite being ‘immunodeficient’ by most measures, produce a rapid burst of high-affinity IgG after infection and this IgG enables the mice to clear the organism more effectively than wild-type mice (which produce more antibody but do so gradually and in a greater range of affinities) [17]. These results suggest the kinetics and focus of B-cell responses can have as great an impact on host defense as the total amount of antibody produced. We are eager to see how broadly applicable these observations will prove to be.

We would offer one final comment on the harnessing of B-cell responses for immunotherapy. As we have briefly reviewed above and elsewhere [1,18,19], B-cell functions extend well beyond the production of antibodies, and touch on nearly every aspect of innate and adaptive immunity, including development of lymphoid organs and of T cells, antigen presentation, regulation of T-cell activation and effector functions. B-cell functions can also determine the impact immunity will have on the target cell or microorganism. Although antibody concentration, isotype, avidity, cytotoxicity or virus neutralization continue to serve as standards for evaluating vaccines and assessing host responses to infection and transplantation, these approaches should not be assumed to represent the spectrum of B-cell responses much less the impact

those responses might have. In populations of transplant recipients, the presence, level and specificity of antibodies against the graft donor may correlate the outcome but in individual subjects, these indices alone mean little. Therefore, we believe the development of new approaches to evaluating the range of B-cell responses will prove pivotal to the harnessing of those responses for the treatment of disease.

Financial & competing interests disclosure

The authors' work was supported by the NIH. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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