Vaccine 31 (2013) 297–305

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

T cell vaccinology: Exploring the known unknowns

Matt A. Burchill[1], Beth A. Tamburini[1], Nathan D. Pennock[1], Jason T. White[1], Jonathan S. Kurche[1], Ross M. Kedl*

Integrated Department of Immunology, University of Colorado Denevr and National Jewish Health, Denver, CO 80206, United States

ARTICLE INFO

Article history:
Received 20 September 2012
Received in revised form 22 October 2012
Accepted 25 October 2012
Available online 6 November 2012

Keywords:
CD8+ T cell
Vaccine
Adjuvant
T cell memory

ABSTRACT

The objective of modern vaccine development is the safe generation of protective long-term immune memory, both prophylactic and therapeutic. Live attenuated vaccines generate potent cellular and humoral immunity [1–3], but numerous problems exist with these vaccines, ranging from production and storage issues to adverse reactions and reversion to virulence. Subunit vaccines are safer, more stable, and more amenable to mass production. However the protection they produce is frequently inferior to live attenuated vaccines and is typically confined to humoral, and not cellular immunity. Unfortunately, there are presently no subunit vaccines available clinically that are effective at eliciting cellular responses let alone cellular memory [4]. This article will provide and overview of areas of investigation that we see as important for the development of vaccines with the capacity to induce robust and enduring cellular immune responses.

Contents

1. Introduction

The importance of T cell immunity to vaccination is at least two-fold. First, though neutralizing antibody is admittedly the reason for the success of the majority of vaccines thus far, this parameter is far less relevant (if not irrelevant) when considering therapeutic vaccination against established diseases such as HIV, Hepatitis C, Mycobacterium tuberculosis (mTB), or cancer. In these situations of chronic infection/disease, it is clear that potent cellular immunity is a prerequisite for vaccine efficacy [5]. Second, even in situations where neutralizing antibody is protective, the biology of the infectious agent may make the generation of cellular immunity far more desirable than just antibody. A good example is influenza where a cellular response against antigens conserved across multiple strains would be expected to protect the host more broadly that the typical yearly vaccine-elicited neutralizing antibody responses against the highly variable HA and NA proteins. Therefore, there is a significant need for the development and implementation of new vaccine paradigms capable of priming robust CD4 and CD8+ T cell immunity.

The production of such a vaccine will require the identification not only of the appropriate antigens to serve as immunologic targets, but also the discovery of robust adjuvants, capable of performing the tasks listed above [6–9]. Following the conceptual leadership of Charlie Janeway [10], all those interested in the generation of adaptive immune responses from vaccination have spent the last 3 decades searching for entities that elicit innate

* Corresponding author at: Department of Immunology, University of Colorado Denver, NJ Health, Goodman Bldg. K825, Denver, CO 80206, United States. Tel.: +1 303 270 2061; fax: +1 303 270 2325.
E-mail address: ross.kedl@ucdenver.edu (R.M. Kedl).
[1] Considered first author contributor.

0264-410X/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2012.10.096

immunity for use as vaccine adjuvants. Numerous advances have been made in the last 10 years regarding the identification of new innate signaling pathways as well as the identification of the agonists/ligands that instigate their stimulation [11–13]. These discoveries have presented the vaccine world with a veritable plethora of agonists and ligands to incorporate into rationally designed vaccine adjuants in the hopes that better days are ahead for the generation of enduring, vaccine elicited cellular responses.

Unfortunately, these advances in innate immunity have not necessarily translated into significant clinical advances in vaccines and/or vaccine adjuvants. Years of exploration have revealed that the mere generation of innate immunity does not guarantee that adaptive immunity will follow. That is, there is a distinction between innate immunity that simply elicits inflammation and innate immunity that effectively transitions into robust adaptive immunity, specifically T cell immunity. The failure to produce advances in vaccine biology commensurate with the explosion of information on innate activating pathways is due, at least in part, to a failure in addressing a number of "known unknowns" (with apologies to Donald Rumsfeld) in vaccine biology. In calling them as such, we recognize that not all of these known unknowns are universally agreed upon as known, unknown or even as unknowns worthy of knowing. Be that as it may, this review will present a short list of vaccinology considerations and the rationale behind why these are important parameters to explore for the purposes of ongoing and future vaccine design and development.

2. Will the real signal 3 please stand up?

It has long been appreciated that additional signals outside of the trimolecular complex (MHC–peptide–antigen) are required for fulminate T cell activation [14]. In the mid 1980s, CD28 was identified, and has since been well characterized, as a required costimulatory molecule for functional T cell responses [15,16]. Through associated kinase activity, ligation of CD28 with either CD80 or CD86 (B71/2) on antigen presenting cells results in upregulated and stabilized IL-2 mRNA expression, IL-2 production, mTOR activation, and subsequent upregulation of the pro-survival factor Bcl-xL [17–19]. Collectively CD28 provided the necessary signal(s) along side of TCR activation for robust T cell proliferation and survival, the so-called 2 signal hypothesis of T cell activation [20].

However, T cells do more than just proliferate, being called upon to express a variety of effector functions ranging from the production of pro- and anti-inflammatory cytokines to lysis of antigen bearing target cells [21,22]. In addition, after pathogen/target clearance, T cells must contract to a memory pool that will remain poised for rapid helper/effector functions upon reintroduction of cognate antigen [23]. The two signal model of T cell activation is not sufficient for providing information that can direct either the effector or memory arms of the response, and thus a minimal "3 signal" model was proposed. By way of analogy, in the dance that is a developing T cell response, signal 1 (MHC–peptide–TCR) serves to promote selection of a capable dance partner, signal 2 (CD28) enhances this recognition and promotes a more firm embrace between the dancers, while signal 3 serves as the music telling the dancers whether they are in a tango, foxtrot, or waltz.

Immunologically, the concept of signal 3 was coined and formalized for CD8+ T cells when Mescher and colleagues proposed that cytokines of the immunological milieu played a deterministic role in the fate of CD8 T cell responses to in vitro activation cultures and adjuvant antigen priming [22]. They and others would go on to show that type I IFN and IL-12 acting through their receptors on the surface of T cells could program both the acute T cell response and the kind and quality of the T cell memory response [24–30]. In the realm of CD4 helper T cell biology this paradigm fits with the ever expanding world of helper T cell differentiation in which specific cytokines direct CD4+ T cell fate into various cytokine producing Th1, Th2, Th17, etc. T cell subsets [31]. Molecularly speaking, the factors capable of providing "signal 3" support were universally inflammatory cytokines, typically involving the induction of STAT1 or STAT4 signaling into the responding T cells [28]. Activation of these signaling modalities eventually culminates in regulating the expression of transcription factors (Tbet, Eomes, RORγT, GATA3) that ultimately shape the fate of the cell [25–27,29,30]. This has been confirmed in numerous model systems where T cells deficient in various cytokine receptors show impairments in primary and secondary responses to certain pathogen challenge or vaccination [23,32].

While the capacity for IL-12 or type 1 I IFN to serve as signal 3 mediators is undisputed, a growing number of observations indicate that these signaling pathways can at times be a liability for the generation of immune memory [26]. Recent studies in both mouse and human indicate a central role for STAT3-inducing cytokines in the development of T cell memory, primarily due to the capacity of STAT3, and subsequent induction of SOCS3, to limit STAT4 activation and downstream Tbet expression [33,34]. Thus, T cell memory is achieved only through the limitation of STAT4/Tbet. Indeed, unrestricted Tbet expression, which is downstream of both STAT1 and STAT4 "signal 3" mediators, has gained a reputation for being too much of a good thing, serving to severely blunt the development of long term memory [35,36]. As immune memory is the object of vaccination, these data question what the optimal signal 3 mediators are in a vaccine setting.

In the search for non-cytokine signaling pathways, various TNF Receptor family members appear to support signal 3 functions in responding T cells [37], specifically under conditions of vaccination in which the generation of memory T cells is preferred over the generation of primary effectors. Recently we published that the generation of immune memory in response to vaccination using a combined TLR/CD40 adjuvant [38,39] is independent of all the usual cytokine signal 3 suspects, instead relying upon the TNFR family members CD27 and OX40 [40]. In these experiments both the primary and the memory CD8+ response is critically dependent upon signals through CD27 principally and residually through OX40. In contrast, the CD4 response to this vaccination is more dependent upon OX40 with a residual dependence on CD70 [41]. TNFR signaling promotes T cell survival through NFkB activation of the pro-survival member Bcl-xL [37,42–45]. Besides contributing to T cell survival and memory formation, van Lier and colleagues showed that CD27 was specifically required for the survival of lower affinity T cells into the memory pool [46]. When present, these lower affinity cells resulted in T cell pool with greater cross reactivity and better immune protection to challenge with a disparate, but related pathogen. Thus TNF receptors, with their capacity to promote the survival of immunity against a more broad diversity of pathogens, may represent a form of "signal 3" that might be specifically preferred during vaccination.

Collectively, the data suggest that the notion of a "signal 3" may have a good deal of flexibility, and it is even likely that signals beyond cytokines or TNF receptors may be competent for supporting complete T cell activation and programming of memory. A true reductionist approach suggests perhaps a 4 signal model consisting of peptide/MHC and CD28 to support initial activation (signals 1 and 2), cytokine mediated expansion and differentiation matched to the inflammatory milieu (signal 3a), and TNFR-mediated survival (signal 3b) of both effectors and long lived memory. A major area of focus for the future should be the exploration and identification of the spectrum of pathways capable of contributing to signals 3a/b and how to best target these for the purposes of vaccine development.