EBioMedicine 2 (2015) 632–633

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Origins of a Vaccine-Induced, Human Anti-HIV-1 Antibody

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A broadly effective HIV-1 vaccine would greatly contribute towards prevention of the 2.1 million new HIV-1 infections estimated to occur annually. Six HIV-1 vaccine efficacy trials in humans have thus far been conducted. Whereas most vaccines showed no efficacy in preventing from HIV-1 infection – and two actually increased infection rates in vaccine recipients – the RV144 Thai phase III HIV-1 vaccine trial is to date the only one to have shown efficacy, albeit marginally (31.2% decrease in HIV-1 acquisition at 42 months post-vaccination) (reviewed in (Kim et al., 2015)). Surely, this level of efficacy is insufficient; but these results gave hope that correlates of protection could be identified and improved upon as a path towards a more effective HIV-1 vaccine. In this issue, Nicely et al. present atomic-level details of the maturation pathway taken by a RV144 vaccine-induced antibody, CH58.

The regimen administered to RV144 Thai trial volunteers consisted of four interspersed ALVAC™-HIV doses (canarypox-based viral vector with env/gag/pol components) boosted twice with AIDSVAX® B/E (bivalent monomeric gp120 protein) over six months (Rerks-Ngarm et al., 2009). Rigorous efforts to uncover correlates of protection in vaccine recipients revealed that IgG binding to a V1/V2 scaffold (HIV-1 gp120 variable loops 1 and 2 displayed on the murine leukemia virus gp70 protein) inversely correlated with infection. Two isolated antibodies from vaccine recipients, CH58 and CH59, bind to lysine 169 in gp120 V2 (Liao et al., 2013), a position implicated by sieve analysis in blocking sequence-matched HIV-1 strains. Interestingly, these antibodies only neutralize HIV-1 weakly, but mediate effective antibody-dependent cell-mediated cytotoxicity (ADCC) as the mechanism to thwart HIV-1.

Upon exposure to foreign antigens, precursor B cells undergo affinity-based selection and hypermutation of variable domains to gain in affinity and proliferate — a process termed affinity maturation. To shed light into the maturation pathway of the RV144 vaccine-induced CH58 antibody, Nicely and colleagues inferred its precursor sequence, and performed comparative structural and biophysical studies of the germline antibody and its mature counterpart. Only 11 mutations separate the precursor sequence from the mature antibody — a maturation pathway driven by the multivalent, prime-boost RV144 vaccine regimen. Conversely, the development of broadly neutralizing antibodies (bnAbs) in natural HIV-1 infection often requires more extensive affinity maturation. As an example, bnAb VRC01, which neutralizes ~90% of circulating HIV-1 isolates, has 66 residue alterations encoded in its variable light and heavy genes (Zhou et al., 2010). The CH58 affinity maturation pathway deepens our understanding of the level of somatic hypermutation achievable by current vaccination technology and serves as a benchmark to evaluate whether re-elicitation of extensively mutated bnAbs like VRC01 might ever be feasible by vaccination.

Structural analysis of the predicted CH58 antibody precursor by Nicely et al. reveals how the paratope is largely structurally pre-configured for gp120 V2 recognition. The precursor light chain complementarity determining region 2 (LCDR2) already contains a Glu–Asp dipeptide motif ideally positioned to recognize basic gp120 V2 residues. Two of the 11 mutations acquired during somatic hypermutation contribute two new salt bridges to V2 residues, and their role in the observed gain in affinity for mature CH58 (from 11.0 μM to 4.6 nM) appears to be predominantly through decreasing off-rates (600-fold decrease in off-rate, and 4-fold increase in on-rate).

The affinity maturation pathway of CH58 described by Nicely and colleagues is a clear example of the antibody precursor paratope being largely pre-configured, and gaining in affinity from few mutations that improve off-rates. In that sense, the CH58-lineage resembles the CH59-lineage (Wiehe et al., 2014), but differs from the maturation pathway observed for some other antibodies. Indeed, conformational diversity, which is not evident in the CH58 precursor, had been previously demonstrated to diversify the antibody germline repertoire and contribute towards molecular recognition of an increased number of antigens when combined with sequence diversity (Wedemayer et al., 1997).

B cell ontogenies describe the evolution of antibody responses. Insights gained from such studies often guide immunogen design strategies that seek to recapitulate or improve elicitation of specific B-cell lineages in vaccination. For example, several bnAbs against the influenza hemagglutinin stem or against the HIV-1 Env receptor binding site (RBS) have been shown to derive from the same germline precursor genes — VH1-69 and VH1-2, respectively (reviewed in (Haynes et al., 2012)). Re-eliciting these protective bnAb responses in vaccination is a highly desirable goal. Recent HIV-1 immunogen-design efforts seeking to target specific B-cell precursors in vaccination successfully initiated the desired germline response (Dosenovic et al., 2015; Jardine et al., 2015). However, germline-targeting might not always be the appropriate immunization strategy. The inherent diversity of the germline repertoire can also result in convergence on immune solutions that arise from different starting points, as recently described for bnAbs against the influenza hemagglutinin RBS (Schmidt et al., 2015).

Will germline-targeting be a viable strategy to broaden the efficacy of anti-HIV-1 antibodies that mediate ADCC, such as those elicited in

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2015.06.016.

http://dx.doi.org/10.1016/j.ebiom.2015.07.019

the RV144 vaccine trial? Such questions can now be tackled in greater depth based on a better understanding of the CH58 antibody-lineage revealed by Nicely and colleagues.

Conflict of Interest

The author declares no conflicts of interest.

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