Dendritic Cell Activation Kinetics and Cancer Immunotherapy

Matteo Bellone, Annalisa Camporeale and Andrea Boni

*J Immunol* 2004; 172:2727-2728; doi: 10.4049/jimmunol.172.5.2727-a

http://www.jimmunol.org/content/172/5/2727.2
Lack of Association between Human Switch Recombination Breakpoints and the Secondary Structure of Targeted DNA Regions

As class switch recombination (CSR) is a region, rather than a site-specific event, a relationship between the recombination breakpoints and the structural character of the switch (S) regions involved has been sought. It has earlier been suggested that CSR preferentially occurs at transitions from a stem to a loop structure in ssDNA (microsites) in S regions from a variety of species (1, 2). However, only a limited number of breakpoints have been analyzed (1, 2). In the October 1, 2003 issue of The Journal of Immunology, Cameron et al. (3) showed that three of the four breakpoints described (Sμ, Se, and Sy) from nasal tissue also mapped to microsites and suggested that their observations represented the first evidence for a structural recognition pattern in primary human B cells. However, we have previously shown, using a large number of Sy breakpoints from in vivo switched human B cells, that the percentage of breakpoints at microsites is not higher than expected by chance (4). We have now reanalyzed our previously published Sy breakpoints (n = 68) and added another 130 Sμ and 62 Se breakpoints, using the standard applied by Tashiro et al. (2). As shown in Table I, the percentage of breakpoints at microsites is not higher than expected by chance (χ² test), even though many S junctions are indeed located at (position 0), or in the proximity of (position 1), these sites (for full data see www.biosc.iki.se/users/qipa/microsites). Therefore, new ways of exploring the role of secondary and tertiary structure of the S regions are required to explain the location of the switch recombination breakpoints.

Qiang Pan-Hammarström, Yaofeng Zhao, and Lennart Hammarström

Division of Clinical Immunology
Department of Laboratory Medicine
Karolinska Institutet at Huddinge Hospital
Stockholm, Sweden

Center for Biotechnology
NOVUM
Huddinge, Sweden

Table I. Occurrence of breakpoints in the proximity of the transitions from stem-to-loop regions in the secondary structure (microsites) in human S regions

<table>
<thead>
<tr>
<th>S Region</th>
<th>Expected (%)</th>
<th>Observed</th>
<th>Expected (%)</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sμ</td>
<td>69</td>
<td>67% (87/130)</td>
<td>90</td>
<td>85% (110/130)</td>
</tr>
<tr>
<td>Sy</td>
<td>44</td>
<td>36% (24/67)</td>
<td>67</td>
<td>69% (46/67)</td>
</tr>
<tr>
<td>Se</td>
<td>55</td>
<td>53% (33/62)</td>
<td>77</td>
<td>68% (42/62)</td>
</tr>
</tbody>
</table>

*Fragments of 200 bp of the Sμ, Sy, or Se regions were folded in regions spanning the switch recombination breakpoints, using the Mfold program developed by M. Zuker. The structure with the lowest free energy of duplex formation was chosen for analysis. When microhomology at the switch junction was observed, the 3’ nucleotide of the upstream breakpoint (Sμ) and the 5’ nucleotide of the downstream breakpoint (Sy or Se) were analyzed. The Sy breakpoints include 42 Sy3 and 26 Sy4 breakpoints, and the Se breakpoints include 42 Se1 and 20 Se2 breakpoints.

Dendritic Cell Activation Kinetics and Cancer Immunotherapy

In a recent paper published in The Journal of Immunology, Watanabe and colleagues (1) report on the impact of dendritic cell (DC) activation kinetics on the in vivo priming of Ag-specific T lymphocytes. Thus, the authors focus on a central issue in DC-based immunotherapy, which has already been addressed both in vitro (2, 3) and in vivo (4), reaching very similar conclusions. Worthy of note, Watanabe and colleagues (1) show that as early as 3 h after anti-CD40 Ab stimulation, DCs already developed into powerful cellular vaccines. We found that DCs produced IL-12 and marginally up-regulated cell surface molecules as early as 15 min after exposure to promaturation stimuli, but as for human DCs (2) the peak of IL-12-producing DCs was reached at 8 h, whereas MHC and costimulatory molecules expression significantly increased only later on (4). Unfortunately neither we (4) nor Watanabe and colleagues (1) compared the therapeutic efficacy of 3-h and 8-h DCs exposed to maturation stimuli, but as for human DCs (2) the peak of IL-12-producing DCs was reached at 8 h, whereas MHC and costimulatory molecules expression significantly increased only later on (4). In a recent paper published in The Journal of Immunology, Watanabe and colleagues (1) report on the impact of dendritic cell (DC) activation kinetics on the in vivo priming of Ag-specific T lymphocytes. Thus, the authors focus on a central issue in DC-based immunotherapy, which has already been addressed both in vitro (2, 3) and in vivo (4), reaching very similar conclusions. Worthy of note, Watanabe and colleagues (1) show that as early as 3 h after anti-CD40 Ab stimulation, DCs already developed into powerful cellular vaccines. We found that DCs produced IL-12 and marginally up-regulated cell surface molecules as early as 15 min after exposure to promaturation stimuli, but as for human DCs (2) the peak of IL-12-producing DCs was reached at 8 h, whereas MHC and costimulatory molecules expression significantly increased only later on (4). Unfortunately neither we (4) nor Watanabe and colleagues (1) compared the therapeutic efficacy of 3-h and 8-h DCs exposed to maturation stimuli, but as for human DCs (2) the peak of IL-12-producing DCs was reached at 8 h, whereas MHC and costimulatory molecules expression significantly increased only later on (4).

Matteo Bellone, Annalisa Camporeale, and Andrea Boni

Cancer Immunotherapy and Gene Therapy Program
Istituto Scientifico H San Raffaele
Milan, Italy

References
References


T Cell-Dependent and Independent Responses

With great interest we have read the recent paper by Khan et al. (1) on the cognate T cell help in the immune response to intact Streptococcus pneumoniae. The authors studied the role of the CD4+ T cells on the IgM and IgG responses specific for the capsular polysaccharide, the cell wall C-polysaccharide, and the pneumococcal surface protein A. In their manuscript they state that, “in responses to intact S. pneumoniae, IgG responses to capsular polysaccharide are strongly dependent on CD4+ T cells and CD40L-dependent costimulation, unlike responses observed for purified soluble polysaccharide Ags”.

Pneumococcal capsular polysaccharides (caps-PS) are classified as T cell-independent Ags type 2 (2). These Ags stimulate Ab production in the absence of MHC class II restricted T cell help, but, nonetheless, they can recruit T cell help (2). It has been previously demonstrated that T cells play a role in the anti-caps-PS Ab response (3, 4). More recently, we showed that the Ab response to soluble caps-PS is dependent on T cells and on the CD40-CD40L interaction (5, 6). Besides, Dullforce et al. (7) showed that administering anti-CD40 mAb to mice along with pneumococcal polysaccharide results in the generation of a strong protective Ab response.

Therefore we think that, contrary to what is claimed by Kahn et al. and to previous observations (8), there is presently enough evidence to state that T cells and CD40-CD40L interaction play a role in the Ab response to caps-PS.

Axel Jeurissen and Xavier Bossuyt

Experimental Laboratory Medicine
University Hospital Leuven
Leuven, Belgium

References


The Authors Respond

The letter by Drs. Jeurissen and Bossuyt challenges the veracity of a statement we made in our recent paper by Khan et al. (1) that IgG responses to purified TI-2 (polysaccharide) Ags are T cell independent, unlike the IgG anti-polysaccharide responses that we observe upon challenge with intact extracellular bacteria, which are critically dependent on CD4+ T cells. They cite their own recently published work (2) and that by B. J. Zegers’ lab (3), although they omit citing the much earlier extensive work from P. J. Baker’s group (for review see Ref. 4), that collectively demonstrate the existence of T amplifier (Ta) and T suppressor (Ts) cells in response to certain purified TI-2 Ags. Indeed, on this basis Jeurissen and Bossuyt wish to conclude that, “the Ab response to soluble capsular polysaccharide is dependent on T cells”. However, as summarized by Baker and Hiraba (4): “Although both types of regulatory T cells are activated after exposure to Ag, their activities are usually counterbalanced. This balance explains why athymic mice make nearly the same Ab response to SSS-III as thymus-bearing mice, and why Ts and Ta have escaped detection for so many years.” Hence, these responses may involve the activation of Ta and Ts cells, but are not collectively dependent on these T cells, a point confirmed through the use of athymic nude or TCR-knockout mice. Our use of the traditional expression “T cell-independent” follows this latter widely accepted understanding (5). In this regard, our observations that IgG anti-polysaccharide responses to intact S. pneumoniae are markedly reduced in athymic nude or TCR-knockout mice, whereas the Ig responses to purified polysaccharide Ags are not (1, 6), underscores a very important mechanistic distinction between these two types of “immunogen”, but does not in any way contradict the many studies on Ta and Ts cells.

The recently published study by Jeurissen and Bossuyt (2) which reports a role for CD40/CD40L interactions in Ig responses to purified pneumococcal polysaccharide (PPS)3, 4, and 19F, while interesting, stands in contrast to many previous studies using the TI-2 Ags, TNP-Ficol, or DNP-Ficol (7), or a more recent study using purified PPS6B (8), that conclude that these Ig responses are independent of CD40/CD40L interactions. The observation that injection of an agonistic anti-CD40 mAb, a potent activator of B cells, DC and macrophages, enhances an in vivo Ig response to a purified TI-2 Ag does not address a potential endogenous role of CD40/CD40L interactions in these responses. Thus, we disagree with the general statement by Jeurissen and Bossuyt that, “there is presently enough evidence to state that . . . CD40-CD40L interaction[s]
play a role in the Ab response to [purified TI-2 Ags]”. Instead, the differences between their published study, and those of others need to be resolved, and thus we should consider this issue as currently controversial.

Clifford M. Snapper
Department of Pathology Uniformed Services
University of the Health Sciences
Bethesda, MD 20814

References


