HAPTEN-SPECIFIC REGULATION OF MEMORY B CELL EXPRESSION

LEONORE A. HERZENBERG, TAKESHI TOKUHISA AND LEONARD A. HERZENBERG
Department of Genetics, Stanford University School of Medicine,
Stanford, California, 94305, USA

The production of high affinity antibody responses requires a regulatory environment that supports both the development and expression of mature memory B cells. In our earlier studies[1,2] we described a variety of parameters that interfere with the development of early (IgD^+) memory B cell populations to mature (IgD^-) memory populations which undergo affinity maturation. Conditions which permit the development of high-affinity memory populations, however, do not assure the production of a high-affinity antibody response. As we have shown recently, response affinity is also determined by a previously unrecognized regulatory system that controls the expression of memory B cells according to Ig combining site and constant region commitment[3-5].

Briefly summarized, this "hapten-specific" system selectively supports or prevents the expression of the individual memory B cells in mature high-affinity memory populations. Consequently, it serves to define the overall spectrum of IgG antibodies produced in T-dependent antibody responses to complex antigens. It can be induced to stably suppress IgG antibody production to the dinitrophenyl (DNP) hapten on commonly used carrier proteins without interfering with the production of IgG antibodies to any of the other (native structural) determinants on these molecules. In addition, it can be induced to selectively suppress the production of high-affinity anti-DNP antibodies and to selectively regulate the production of individual isotypes (Ig subclasses) with anti-DNP combining sites. Thus, the individually specific regulatory elements that comprise the system provide the basic machinery required to prevent the production of any or all of the antibodies potentially present in broadly heterogeneous IgG responses.

These elements, however, can also be induced to support antibody production. Furthermore, when induced into this "positive" configuration, they largely prevent suppression-induction for the antibodies they support and consequently stabilize the animal to produce rather than prevent production of the antibodies they regulate. As a whole, therefore, the hapten-specific system provides a

bistable regulatory capability which permits initial immunization conditions to define the spectrum of variable region (combining site) and constant region (isotype/allotype) structures produced in primary and subsequent antibody responses to a given determinant.

The cellular mechanisms responsible for inducing and mediating suppression in the hapten-specific system have not been defined as such; however, for the most part, these mechanisms appear to be well known, albeit in a different context. The suppression-effector mechanism combines key properties previously defined for idiotype and allotype regulatory systems (i.e., the selective regulation of antibody production according to Ig variable region and constant region determinants and the control of memory B cell expression rather than development). Similarly, the major suppression-induction mechanism apparently represents the actual function of the carrier-specific suppressor T cells studied in many laboratories (i.e., our studies[5] strongly suggest that these suppressor cells control responses by inducing hapten-specific suppression rather than depleting carrier-specific help). In addition, allotype suppression contributes to the induction of hapten-specific suppression[5]. Thus, our studies essentially introduce a new regulatory system whose properties derive from the functional integration of mechanisms that have been independently explored for many years.

These findings suggest the need for a radical revision of current concepts of antibody response regulation. They define a centrally operating regulatory system that independently controls the expression of each of the memory B cell clones that arise following antigenic stimulation. This system provides a major (and possibly the only) effector mechanism through which carrier-specific regulatory cells influence the composition of such responses. It may also be central (we suggest) to IR gene control and the maintenance of immunologic tolerance[5].

The properties of this hapten-specific system show a remarkable consistency with the properties of the integrative and bistable regulatory system defined by the theoretical regulatory "circuits" we recently proposed[6]. That is, like the CORE circuits in the model, the central elements of the hapten-specific system regulate B cell expression according to Ig commitment, provide bistable "configurational" memory and integrate influences from a variety of other regulatory mechanisms to determine which of the antigen-reactive B cell clones capable of participating in a response will be permitted to do so. Thus this circuit model, which predates the discovery of the hapten-specific system,

offers a plausible set of cell interactions on which hapten-specific regulation could be based.

ACKNOWLEDGEMENTS

We wish to thank Mr. F. Timothy Gadus for expert technical assistance. This work supported, in part, by grants from the National Institutes of Health, HD-01287 and AI-08917. Dr. Tokuhisa's current address is: Laboratories for Immunology, School of Medicine, Chiba University, 1-8-1 Inohana, Chiba, JAPAN, 280.

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