Allotype suppression and epitope-specific regulation

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In neonatal (A × B) F1 mice, injections of maternal (A strain) antibody to the Ig allotype of the paternal (B) strain chronically suppress the production of antibodies with the B-strain allotype. Here Leonore Herzenberg describes how, in such animals, this form of suppression influences the control of antibody responses to a thymus-dependent antigen that is subsequently encountered.

The 'chronic allotype-suppression' system* occupies a peculiar niche in immunoregulatory history. Although often considered esoteric, this system (see Tables I and II) has actually been one of the major contributors to the development of current concepts of how antibody responses are regulated in normal animals. The initial acceptance of suppressor T cells as functional regulatory agents, for example, was based to a considerable extent on the strong and specific suppression demonstrable with allotype suppressor T cells in adoptive 'co-transfer' assays[1-4]. Furthermore, many of the commonly known properties of suppressor T cells were first identified in allotype suppression studies[5-10].

In the early 1970s, allotype suppressor T cells were used to demonstrate that suppressor T cells carry Lyt-2 determinants[8] and to define the first locus in the *I-J* subregion of the mouse major histocompatibility complex (MHC)[9]. Similarly, these cells were used in studies that provided the first evidence for 'Ig-specific' helper T cell activity in heterogeneous antibody responses, and the depletion of helper T cell activity by suppressor T cells and soluble suppressive factors[5-8,10,11]. However, although these ideas rapidly became part of the interpretation of more commonly studied regulatory systems (carrier-specific, idiotype-specific, *Ir* gene controlled), allotype suppression and selective allotype regulation in general remained mostly outside mainstream thinking on the mechanisms that normally control antibody production.

Our studies in this area nonetheless continue, and, most recently led to the discovery of a central Igh-restricted regulatory system that plays a key role in determining the magnitude, affinity, specificity and Igh (allotype/isotype) representation in primary and anamnestic (memory) responses in normal animals[12-18]. These studies implicate Igh-restricted regulation in all T-dependent antibody responses and, furthermore, demonstrate a direct connection between the initial suppression of allotype production and the subsequent control of allotype-marked antibody responses to individual antigens.

*Studies of the cells and mechanisms involved in the chronic suppression of Igh-1b (IgG2a) allotype production induced by exposing (BALB/c × SJL)F1 mice perinatally to antibody to the paternal Igh-1b allotype: various aspects of this regulatory system have been examined in our laboratory over the last 15 years by Ethel Jacobson, Roy Riblet, Charles Metzler, Ko Okumura, Donal Murphy, Samuel Black, Vernon Oi, Kyoko Hayakawa, David Parks, Takeshi Tokuhisa and Leonard A. Herzenberg, who has been a continuous and valuable collaborator in this work.

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As we have now shown, an 'epitope-specific' regulatory system† operative in all mouse strains selectively controls antibody responses to individual epitopes on complex antigens such as DNP-KLH (2,4-dinitrophenyl hapten on keyhole limpet hemocyanin). This system regulates the expression (rather than the development) of memory B cells; it can be induced to either persistently suppress or persistently support antibody production; and it consists of a series of Igh-restricted, epitope-specific elements individually dedicated to regulating the production of antibody molecules that have the same combining-site specificity and Igh constant-region structure[12-18].

Allotype suppression is itself an Igh-restricted regulatory mechanism that controls memory B-cell expression[4,6,8]. However, it lacks antigen specificity: allotype suppressor T cells taken from unprimed donors suppress Igh-1b (IgG2a) allotype adoptive secondary responses by cells from donors primed with DNP-KLH or a variety of other antigens. Furthermore, these suppressor T cells are induced in neonates in the absence of exogenously supplied antigens[4]. Nevertheless, as we have now shown, the allotype suppression mechanism can specifically interfere with the long-term production of individual Igh-1b anti-epitope responses by inducing the epitope-specific system to suppress such responses[17].

Characteristics of allotype suppression mechanisms

In the original studies defining 'chronic' allotype suppression in (BALB/c × SJL)F1 mice, we followed a suppression-induction protocol similar to protocols used previously to induce allotype suppression in rabbits and in other mouse hybrids, i.e. perinatal exposure to maternal (BALB/c) antibody to the paternal (SJL) Igh-1b allotype[4]. More recently, we showed that typical chronic suppression can be equally well induced by injecting neonates with some (but not all) monoclonal antibodies to Igh-1b (1b) allotypic determinants[19], or by injecting conventional antibodies to allotypic or isotypic determinants on IgM[20].

Curiously, however, the injection of monoclonal antibody to IgD (Igh-5b) allotypic determinants induces an Igh-restricted suppression of IgG antibody production that has entirely different properties[21,22]. In essence, this

†We have previously referred to this system as hapten-specific, using the term 'hapten' in its more general sense (synonymous with epitope) to indicate a relatively small structure which induces antibody production when presented on a larger (carrier) molecule. The term 'hapten', however, is also commonly used to distinguish artificially added structures such as the dinitrophenyl phenyl group (DNP) from the native epitopes on a carrier molecule (antigen). Therefore, to avoid ambiguity, we have now substituted the term 'epitope-specific' for the previous nomenclature.

TABLE I. Correspondence between immunoglobulin heavy-chain (Igh) constant-region isotypes and allotypes

		Igh isotype (subclass)		
		IgG2a	IgG1	IgD
Locus name	All strains	*Igh-1*	*Igh-4*	*Igh-5*
Alleles	BALB/c	*1a/1a*[a]	*4a/4a*	*5a/5a*
	SJL	*1b/1b*	*4b/4b*	*5b/5b*
	BALB/c × SJL	*1a/1b*	*4a/4b*	*5a/5b*

[a]Full allele names: *Igh-1a*, etc.

anti-IgD induced suppression is more like the allotype suppression induced in rabbits than either the short-term ('acute') suppression that anti-allotype and anti-isotype antibodies induce in most mouse strains, or the chronic suppression induced in (BALB/c × SJL) mice by antibodies to determinants IgG2a or IgM.

Chronic allotype suppression is characterized by the neonatal appearance of allotype suppressor T cells that suppress production of Igh-1b immunoglobulins until the mice reach about 10 weeks of age (see Table II). Nearly all of the mice then initiate 1b allotype production and many achieve normal allotype levels in their sera. Furthermore, they produce normal 1b antibody responses to antigens introduced at this time. This remission, which lasts for about one or two months, is due to the temporary accession of what might now be called 'contra-suppressor' T cells[23] that actively prevent allotype suppressor T cells from suppressing 1b antibody production (Okumura and Herzenberg, unpublished observations).

1b allotype production generally terminates when the mice reach 20–24 weeks of age and the allotype suppressor T cells once again become the dominant regulatory force[4]. Most of our earlier adoptive transfer studies were conducted with cells taken from these older (chronically suppressed) mice; however, we have also successfully transferred specific suppression for 1b antibody production with T cells taken from young allotype-suppressed mice at various times prior to the onset of remission (from 2 weeks of age onwards) (Ref. 21 and Okumura, Tokuhisa and Herzenberg, unpublished observations).

Epitope-specific suppression in allotype-suppressed and normal mice

The studies that unexpectedly led to the identification of the epitope-specific regulatory system began as an attempt to determine whether the 1b memory B cells generated in young allotype-suppressed mice could be stimulated to produce a normal *in-situ* secondary response after the onset of remission. We primed a series of these young mice and age-matched controls with KLH or DNP-KLH, then restimulated them with either DNP-KLH or DNP-CGG (DNP on chicken gamma globulin) after the allotype-suppressed mice began to produce detectable serum 1b allotype levels.

The responses produced after the first immunization were largely predictable on the basis of previous findings. All animals developed equivalent memory B cell populations (measured in adoptive assays); all animals produced comparable 1a and other IgG isotype responses; control and remission-phase animals produced normal 1b primary antibody responses; and actively suppressed mice that initiated 1b production later than one or two weeks after priming failed to produce 1b antibody responses to either the DNP or KLH epitopes on the priming antigen (see Table III).

TABLE II. Characteristics of chronic allotype suppression

	IgG2a allotype serum levels in (BALB/c × SJL)F1 mice[a] (*Igh-1a/Igh-1b* allotype heterozygotes)			
	Mothers immune to Igh-1b[b]		Normal mothers	
Suppression status	Igh-1a	Igh-1b	Igh-1a	Igh-1b
Active 'acute' phase (<14 weeks old)	>500	<10	>500	>500
Remission (16–20 weeks old)	>500	>500	>500	>500
Active 'chronic' phase	>500	<10	>500	>500

[a]μg allotype/ml serum.
[b]Similar results obtained by injecting neonates with monoclonal or conventional antibodies to Igh-1b.

TABLE III. Allotype-suppressed mice produce normal Igh-1b antibody responses if primed during remission

Allotype-suppression status when primed[a]	Antigen	IgG2a antibody responses[b] Anti-DNP (μg ml^{-1}) Igh-1a	Igh-1b	Anti-KLH (units) Igh-1a	Igh-1b
Active	DNP-KLH	+	↓	+	↓
Remission	DNP-KLH	+	+	+	+
Control	DNP-KLH	+	+	+	+

[a](BALB/c × SJL) F1 mice. Actively suppressed animals had less than 2% of the amount of Igh-1b found in sera from remission and age-matched control animals (>500 μg ml^{-1}). Controls were not exposed to maternal anti-Igh-1b.
[b]Serum antibody levels measured by RIA two weeks after priming. + : primary antibody response level (For DNP: 10–30 μg ml^{-1}, mean affinity constant (Ka) = 10^7 M^{-1}).
↓ : suppressed response level (For DNP: <10 μg ml^{-1}, mean Ka = 10^6 M^{-1}).
+ : 100 μg DNP-KLH on alum.

The responses produced after the second immunization, however, defied interpretation according to current immunological dogma. These responses, summarized in Table IV, reduce to three basic findings:

(1) Priming with DNP-KLH while the allotype-suppression mechanism is active induces a persistent, Igh-restricted suppression for 1b anti-DNP and 1b anti-KLH antibody responses, i.e. responses to the epitopes on the priming antigen remain suppressed when the allotype-suppression mechanism itself later becomes dormant (during remission).

(2) The effector mechanism responsible for this suppression is epitope-specific in that it suppresses responses to DNP presented subsequently on the same carrier (DNP-KLH) or on an unrelated carrier molecule (DNP-CGG).

(3) Priming either allotype-suppressed or normal animals with KLH and immunizing subsequently with DNP-KLH (carrier/hapten-carrier immunization) also induces a persistent epitope-specific suppression; however, this suppression affects all IgG isotype and allotype responses equally and is limited to preventing IgG anti-DNP responses.

The major differences between the epitope-specific suppression induced in allotype-suppressed mice and that induced by the carrier/hapten-carrier immunization sequence thus lie in the subset of antibody responses which are suppressed. The carrier/hapten-carrier mechanism, which operates in response to 'new' haptenic determinants presented on antigens to which the animal has already been primed, induces a suppression which specifically prevents antibody production to the added hapten on the carrier but extends to all (IgG) allotype and isotype responses produced to this hapten.

The mechanism that induces (epitope-specific) suppression in allotype-suppressed mice, in contrast, operates in response to epitopes 'seen' on a priming antigen. It therefore induces a suppression that extends to all epitopes on the antigen, but is restricted to preventing 1b antibody responses to those epitopes. Thus, suppression is induced for 1b anti-DNP responses without hampering 1a or other isotype anti-DNP responses, or 1b responses to other epitopes.

Epitope-specific regulation is bistable

The 'mix and match' induction of suppression described above demonstrates that the epitope-specific regulation is mediated by independently inducible Igh-restricted elements. These elements individually control the production of antibodies that have similar combining specificity and the same Igh constant region. In addition, these findings show that the suppression-induction mechanisms active in the immunological environment when an epitope is first introduced can dictate the initial and subsequent responses that will be permitted for that epitope[14–16].

The activity of these suppression-induction mechanisms, however, is balanced by another set of mechanisms which induce epitope-specific regulatory elements to provide stable support, rather than stable suppression, for antibody production[18,24]. The contrast between the almost universal suppression for IgG anti-DNP responses obtained in KLH/DNP-KLH/DNP-CGG immunized animals and the occasional, Igh-restricted suppression obtained when the immunization sequence is permuted to KLH/DNP-CGG/DNP-KLH[18] demonstrates that the initiation of antibody production impairs subsequent suppression induction and vice versa. Thus, a substantially stronger stimulus is required to induce antibody production once suppression has been induced, or to induce suppression once antibody production has been established.

These findings indicate that the individual epitope-specific elements are bistable. That is, an element can be induced initially to either suppress or support antibody production and, once so induced, will actively resist subsequent induction (shifting) to the alternate state[18,24]. Thus, the potential for continued production of a given anti-epitope response is largely determined by the conditions influencing the initial response to that epitope.

The first few days after priming are critical for determining the characteristics of antibody responses to epitopes presented on the priming antigen, since suppression tends to be induced for such responses unless the epitope-specific system is rapidly induced to support them. That is, when the induction of support for a given response fails (either because regulatory conditions dictate the failure or because the epitope was not present on the priming antigen), the epitope-specific elements that control the response remain vulnerable. They can therefore be induced to suppress antibody production once the carrier-specific suppressor T cells[25] that induce such suppression mature to full function (shortly after priming)[13,14,17].

The differences in the scope of the suppression induced by immunization during active allotype suppression, and by carrier/hapten-carrier immunization, are explicable in terms of this bistable regulatory mechanism. The specific suppression of anti-DNP responses in carrier/hapten-carrier immunized animals is due to an antigen-specific mechanism, i.e. the initial absence of the DNP hapten

TABLE IV. Antibody responses are selectively controlled by an allotype-restricted epitope-specific system

Allotype-suppression status (when immunized)[a]				Igh-1 (IgG2a) antibody responses (after second immunization)[b]					
First immunization[+]		Second immunization[+]		Anti-DNP ($\mu g\ ml^{-1}$)		Anti-KLH (units)		Anti-CGG (units)	
Status	Antigen	Status	Antigen	1a	1b	1a	1b	1a	1b
Active	DK	Remission	DK	+++	↓	+++	↓		
Active	DK	Remission	DC	+++	↓			+	+
Remission	DK	Remission	DC	+++	+++			+	+
Control	DK	Control	DK	+++	+++	++	+++		
Active	K	Remission	DK	↓	↓	+++	↓		
Remission	K	Remission	DK	↓	↓	+++	+++		
Control	K	Control	DK	↓	↓	+++	+++		
Control	K	Control	DC	+	+			+	+
Control	C	Control	DK	+	+	+	+		
Control[c]	K/DK	Control	DC	↓				+	
Control[c]	DC/K	Control	DK	(↓ - +++)[c]		+++			

[a]K: KLH; DK: DNP-KLH; C: CGG; DC: DNP-CGG; allotype-suppression status, see legend for Table III.

[b]Serum antibody levels (RIA) two weeks after the second antigenic stimulation. +++ : secondary antibody response level (For DNP: >80 $\mu g\ ml^{-1}$, mean affinity constant (Ka) $>5 \cdot \times 10^{7}\ M^{-1}$). ↓ and + : see legend for Table III.

[c]BALB/c (*Igh-1a* homozygotes); IgG2a, IgG2b and IgG3 responses were suppressed in about half the DC/K/DK animals and no IgG1 responses were suppressed.

+ : 100μg of indicated antigen injected i.p. on alum.

from the priming antigen (carrier) while support is being induced for antibody responses to priming-antigen epitopes, and the subsequent presentation of DNP on the antigen once the maturation of carrier-specific suppressor T cells is complete. Therefore, anti-DNP responses of all IgG isotypes and allotypes are suppressed while anti-carrier responses proceed normally.

The specific suppression of 1b antibody responses to priming-antigen epitopes induced in allotype-suppressed mice, in contrast, is due to the presence of allotype-suppressor T cells. These T cells specifically prevent the normal initiation of 1b antibody responses and therefore leave the epitope-specific elements controlling these responses vulnerable to suppression induction. Therefore, priming allotype-suppressed mice with DNP-KLH results in the induction of suppression for 1b antibody responses to DNP and KLH epitopes, but permits the normal progress of these responses in other allotypes and isotypes.

Priming allotype-suppressed mice with KLH similarly induces specific suppression for 1b anti-KLH responses. Thus, the responses obtained when these mice are subsequently immunized with DNP-KLH reflect the combined suppression-induction potential of the allotype-suppression mechanism and carrier/hapten-carrier immunization: all IgG isotype and allotype responses to DNP are suppressed, 1b anti-KLH responses are also suppressed, and all other isotype and allotype responses to KLH proceed normally (see Table IV). Therefore, although the data from this series of experiments initially appears confusing, it reduces to a consistent series of observations explicable by the bistable operation of a central, Igh-restricted, epitope-specific regulatory system.

Some time ago, we presented a theoretical set of integrated regulatory 'cell circuit' interactions capable of providing bistable regulation for allotype-marked antibody responses to individual epitopes[26]. This model, which (in hindsight) could have been used to predict the findings discussed here, offers a plausible cellular mechanism that would permit the individually specific regulatory elements we have described to maintain their initially induced state and thereby provide stable support or suppression for antibody production. In addition, it presents a detailed discussion of allotype-restricted regulation which, although it requires up-dating, is useful as a framework for considering our current findings.

Originally, we were somewhat hesitant about including allotype-suppression circuitry in this model, largely because there was so little evidence at the time indicating that Igh-restricted regulatory mechanisms were of any importance except when animals were exposed perinatally to maternal anti-allotype antisera. Recently, however, a number of reports have appeared which describe requirements for Igh-haplotype matching between regulatory and effector-cell populations to permit optimal effector function in normal mice (for examples, see Refs 27–29). Furthermore, our own studies on epitope-specific regulation in normal allotype heterozygotes demonstrate discordance in the regulation of the two allotype responses produced by individual animals. The degree of this discordance was sufficient to suggest that isotype representation in antibody responses is normally controlled by Igh-restricted regulatory elements that recognize allotypic, rather than isotypic, determinants.

Allotypic determinants and isotypic determinants are equally useful for identifying isotypes for regulatory purposes, since nearly all allotypic determinants are unique to the individual isotype on which they are found[30]. In fact, in allotype homozygotes, these two types of determinants are formally equivalent. Thus, since the epitope-specific system is clearly capable of regulating allotype representation in antibody responses, the simplest hypothesis suggests that individual isotype responses are regulated by allotype-restricted epitope-specific elements. These elements tend to operate concordantly for a given isotype unless stimulatory conditions induce the system to uniquely suppress production of antibodies carrying a particular allotype.

These considerations introduce a new perspective to the individualization of antibody responses that occurs, for example, in animals producing antibodies to phylogenetically distinguishable epitopes on antigens like KLH and CGG. The varied specificity and isotype representation in responses produced by such animals has commonly been attributed to the selective expansion of different memory B cell clones (i.e. to 'clonal dominance'). However, although selective pressures are clearly capable of channelling memory B cell populations, individual differences in antibody responses can be explained equally well (or perhaps better) by the bistable, epitope-specific, regulation of memory B cell expression. These differences most likely reflect statistical fluctuations in the outcome of the initial race between the induction of stable support for responses to the epitopes on the antigen, and the functional maturation of carrier-specific suppressor T cell populations capable of inducing suppression for such responses[18].

Thus (returning to our initial thesis), although the allotype-suppression system is sometimes considered esoteric, the regulatory mechanisms revealed by studies with this system have proved broadly relevant. In the current instance, such studies have revealed an epitope-specific regulatory system that controls antibody production in normal animals. It also provides a mechanism through which initial immunization conditions can exert a prolonged influence on the characteristics of subsequent antibody responses to the individual epitopes on a complex antigen.

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Human neoplastic B cells: monoclonal models of B-cell differentiation

Tadamitsu Kishimoto

Clones of normal antigen-specific B cells are not yet available but tumors derived from B cells are models of such clones and can be analysed biochemically and functionally. Here Tadamitsu Kishimoto discusses the value of these tumors in the study of B-cell activation

Membrane-bound immunoglobulins (sIgs) serve as antigen-specific receptors on the surface of B lymphocytes and the binding of a given antigen with a sIg initiates a complex series of activation processes which transform B lymphocytes into Ig-producing cells. Despite intensive investigation, the subcellular biochemical mechanisms involved in the triggering and regulation of immunocompetent cells remain poorly understood. One of the central problems in analysing these events is the diversity of cell types in the immune system and the complexity of interactions between them. This diversity is reflected not only in the large repertoire of antigenic specificities expressed by lymphocytes but also in the many subsets of lymphocytes with distinct functions.

Tumors derived from cells of the immune system are models of clones of immune cells and can be subjected to biochemical and molecular analysis. The effect of external signals on the differentiation of these cells is especially useful for the molecular analysis of the signalling involved in lymphocyte activation. The influence of external signals on neoplastic B cells has been demonstrated in murine and human systems. A carcinogen-induced murine pre-B cell line, 70Z/3, which had an intracellular μ-chain but no κ-chains, could produce κ-chain and express surface IgM when stimulated with lipopolysaccharide (LPS)[1,2]. Another spontaneous leukemic B-cell line from BALB/c mice, BCL_1, secreted IgM on stimulation with LPS[3] or on stimulation with anti-Ig and T-cell factors[4].

B-lymphocyte leukemias in humans have been extensively studied with respect to sIg and allo-antigen expression[5]. Recently, several laboratories have attempted to induce the differentiation of leukemic B cells into Ig-producing cells by providing external signals, such as mitogens[6,7], allogeneic T cells[8,9] or T-cell-derived helper factors[10]. In this review, I will describe Ig production in human leukemic B cells and Epstein-Barr (EB) virus-transformed B-cell lines and discuss the cellular and molecular mechanisms of the activation of Ig production in B cells.

Human leukemic B cells

Studies of human B-cell leukemias have demonstrated that the malignant cells are clonal in nature and that the Ig expressed or secreted is limited to the expression of a single V_H and V_L region in each population. Thus, Fu *et al.* showed that, in certain cases of chronic lymphocytic leukemia associated with monoclonal immunoglobulins in the serum, the sIg of the leukemic cells was idiotypically

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