

IF WE WERE TO AGREE THAT....., THEN.....

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IF WE WERE TO AGREE THAT:

1 - the effector output of the “adaptive” immune system is biodestructive and ridding, THEN a mechanism to distinguish “Self” from “Nonself” is obligatory [*pro* [1-3]; *con* [4-8]].

2 - the expression of an effective effector function by the “adaptive” immune system requires two sets of decisions, Decision 1 (the sorting of the repertoire) and Decision 2 (the regulation of effector class), THEN the Self-Nonself discrimination is defined by Decision 1, not Decision 2 [*pro*[9-12]; *con* [13-15]].

3 - the “adaptive” immune system can recognize a significant portion of the pathogenic universe to which the “innate” immune system is blind, THEN both Decisions 1 and 2 must be somatically determined (i.e., dependent on the adaptive, not innate, immune system repertoire) [*pro* [16, 17]; *con* [15, 18]].

4 - the “adaptive” immune repertoire is large, random and somatically generated, THEN it must be sorted by a somatic process into those specificities (anti-Self) which, if expressed, would debilitate the host and those specificities (anti-Nonself) which, if not expressed, would lead to the death of the host by infection (Decision 1). The anti-Self specificities must be purged from the repertoire, leaving anti-Nonself as the residue [*pro* [17, 19]; *con* [5, 7, 8]].

5 - the APC is unable to make a Self-Nonself discrimination because it presents both self and nonself peptides, THEN the effector T-helper (eTh), not the APC (costimulation, interleukins, etc.), must be the source of the antigen-specific activating second signal for antigen-responsive T-cells [*pro* [20-23]; *con* [24-28]].

6 - the sufficiency or insufficiency of regulatory eTh anti-NonselF determines whether an antigen-responsive cell is activated or inactivated, THEN the eTh anti-NonselF must arise by a NonselF antigen-independent pathway [*pro* [2, 20, 21, 29]; *con* [30-32]].

7 - the difference between establishment of unresponsiveness in an immature and mature immune system is due to the insufficiency or sufficiency of eTh, THEN the mechanisms of unresponsiveness established in the face of a sufficiency of eTh are not extrapolatable to the mechanisms for the sorting of the repertoire (Decision 1) nor are they "failsafe" for the Self-NonselF discrimination. They deal with Decision 2, the regulation of effector output [*pro* [2, 3, 29, 33]; *con* [34]].

8 - the repertoire of the regulatory T-suppressor is somatically selected to be anti-NonselF, THEN suppression cannot determine Decision 1, the sorting of the repertoire (the Self-NonselF discrimination); it must play its role at the level of Decision 2 (the regulation of effector class) [*pro* [35, 36]; *con* [37-39]]

9 - the TCR encodes two repertoires, one, anti-R, recognizing allele-specific determinants on MHC-encoded restricting elements (R), the other (anti-P) recognizing peptides (P) bound to them, THEN anti-R must be germline-selected, anti-P must be somatically selected, positive selection and alloreactivity must be peptide unspecific, whereas inactivation (negative selection) and activation require restrictive recognition of peptide (peptide specific) [*pro* [40-43]; *con* [44-46]]

10 - the (NDN)_H region of the BCR was evolutionarily selected to function as framework, not as complementarity-determining, THEN...the primary humoral

repertoire is composed of a small high copy number set and a large low copy number set, which synergize for function [*pro* [47-51]; *con* [52, 53]].

11 - mouse and human (or hummingbird and elephant) are, as individuals, equally protected against infection, THEN their immune systems must be made up of iterated units each of which expresses the protective potential of the whole [*pro* [48, 50, 51, 54, 55]; *con* [56]].

The “if we agree that...” statement is debatable; the “THEN...” part is a consequence, largely logic. However, because the “if we agree that...” statement is reasonably defensible (see *pro* references), a good basis for discussion is established.

These “if we agree that...” postulates rule out, if correct, a widely accepted set of assumptions about “adaptive” immune behavior, among them that:

1 -germline-encoded elements, particularly those of the “innate” system, determine the Self-Nonself discrimination (Decision 1) (i.e., pathogenicity [13], danger [57], localization [58], dose [59], exhaustion [60], etc.).

2 - “dominant unresponsiveness” or suppression (as well as an idiotypic network) regulates the Self-Nonself discrimination [61].

3 - the functioning cognitive repertoires of T and B cells are transcendental [52].

4 - the APC, not eTh, is the source of the second signal required for activation of antigen-responsive T-cells [24-28, 30-32].

The “if we agree that....” postulates point to the importance of experimentally determining:

1 - the origin of the “primer” effector T-helper required to initiate induction of T-helpers [20, 21].

2 - the origin of the “primer” antibody required for uptake of antigen for processing by the APC [33].

3 - whether a conformational change in the TCR/BCR initiates signaling [9, 47, 62].

4 - whether peptide acts as an obligatory specificity element for positive selection of the TCR [41, 43].

5 - whether the repertoire of the regulatory T-suppressor is somatically selected to be anti-Self or anti-Nonself [36].

6 - whether $(NDN)_H$ plays an evolutionarily selected role as framework or as CDR3 [52].

Lastly, the “if we agree that....” postulates permit the introduction of a novel set of concepts into our thinking, for example:

1 - the “Protecton” [47]

2 - the “Tritope” TCR [40-43]

3 - the “signaling patch” [63]

4 - the “Eliminon” [63]

5 - the “primer” pathways [2, 20, 21, 33]

6 - the “Specificity Index” [50, 51, 55]

7 - the "Adapton" [64], the somatic mechanism for the selection of an effective effector function.

Validly competing frameworks are essential if we are to progress; this is an attempt to delineate two of them.

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