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## A Possible Mechanism of Abrogating Progression of Web Beyond Anti-Idiotypic Antibody and a Non Traditional Pathway of Complement Activation

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[Figure 1 Assured Mutual Destruction by complement](#)

[Figure 2 Assured Mutual Destruction by ADCC](#)

# A Possible Mechanism of Abrogating Progression of Web Beyond Anti-Idiotypic Antibody and a Non Traditional Pathway of Complement Activation

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## Abstract

The progression of immune response is currently believed to give rise to anti-anti-idiotypic antibodies. This new hypothesis offers an explanation for the termination or abrogation of potentially endless progression of immune response after the elimination of antigen from the system.

## Background

It is presumed that the formation of antibodies complementary to antibodies under normal conditions of natural exposure to antigen continues beyond anti-idiotypic antibodies leading to anti-anti-idiotypic antibodies [1,2]. Presently there is no logical explanation against this notion. The complement is activated by classical pathway only if the antibody has bound an antigen. On the other hand, antibody is not required in complement activation by the alternative pathway. However, these pathways do not elaborate on any interaction of complement with the idiotypic network in the absence of antigen.

## Results

I propose here a pathway of complement activation which is different from the currently accepted classical and alternative pathways of complement activation. This involves complement activation after pairing of complementary surface immunoglobulins (i.e. idiotypic and anti-idiotypic antibodies) on B cells in the absence of antigen. By definition, the two known traditional pathways do not cover this possibility. I, therefore, propose to call this third pathway as neo-classical pathway of complement activation.

It is known that the antigen – specific immune response may progress even after the elimination of the antigen due to the generation of anti-idiotypic antibodies against the antigen – binding site associated idiotopes. However, if the idiotypic and anti-idiotypic antibodies continue to stimulate each other's production endlessly, it could lead to

exhaustion of resources for other immune responses and harmful consequences for the host.

According to my hypothesis, following engagement of idiotypic and anti-idiotypic antibodies on the surface of respective immunoglobulin bearing B lymphocytes, the complement may get activated by both the surface immunoglobulins and may cause the lysis of respective target B cells through the formation of membrane attack complexes (MAC). Such assured mutual destruction (AMD) may keep a check on undesirable and potentially endless proliferation of complementary B cells (Fig. 1.).

Antibody dependent cellular cytotoxicity (ADCC) – mediated killing of idiotypic antibody bearing B lymphocytes by anti-idiotypic antibody – guided ADCC effector killer cells and of anti-idiotypic antibody bearing lymphocytes by idiotypic antibody – guided ADCC effector killer cells could also be another modality for assured mutual destruction of antibody bearing B cells by the secreted form of complementary antibody (Fig. 2.). This may take care of cells refractory to complement mediated lysis (e.g. cells protected with complement regulatory proteins). It has already been shown experimentally earlier by several researchers that monoclonal antibodies can effect tumor cell killing by activating complement-mediated plus cell-mediated antibody-dependent cytotoxicities. Antitumor antibodies belonging to subclasses such as mouse IgG2a, mouse IgG3, or mouse-human IgG1 chimeric have been used successfully in clinical trials [3, 4].

Similar mechanism could be envisaged for lysis of surface idiotype / anti – idiotype immunoglobulin bearing B cells by idiotype / anti – idiotype – reactive cytotoxic T lymphocytes as well as for suppression of surface immunoglobulin bearing B cells by secreted complementary antibody induced through Fc receptor bearing suppressor cells.

Such assured mutual destruction of immunoglobulin – bearing B lymphocytes by complementary antibody in the form of surface immunoglobulins through complement activation or in the form of secreted immunoglobulins through ADCC should be sufficient to ensure that the antibody formation does not progress beyond the level of second antibody (i.e. anti-idiotypic antibody). Thus the formation of anti-anti-idiotypic

antibody and so on, as believed by some researchers [2, 4], may not be happening in vivo under natural conditions (of course, by experimental immunization with idiotypic antibody it is possible to raise anti-idiotypic antibody which may lead to a complementary (anti-anti-idiotypic) antibody and by injecting anti-idiotypic antibody it is possible to raise (anti-anti-idiotypic) antibody, which do not qualify for being natural third antibody of the idiotypic cascade). This regulation seems logical as it would be economic and resource saving for the immune system of the individual host.

B cells which escape destruction because of complement regulatory proteins or formation of immunoglobulins or B cells engaged in low affinity interactions (e.g. through framework associated idiotopes, not located in antigen binding site of immunoglobulin) may be prevented from antigen binding site associated idiotypic- antiidiotypic pairing and may possibly lead to memory B cells. Such cells may be incompletely activated so are unable to divide, but nevertheless may express some markers associated with activated cells. Such cells possibly fall a little short of being tolerized, do not undergo apoptosis, and may revert to fully activated state upon encountering antigen with a high affinity later in life. Memory cells are indeed known to share some markers with activated cells.

## Abbreviation(s)

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ADCC = Antibody dependent cellular cytotoxicity

AMD = assured mutual destruction

MAC = membrane attack complex

## References

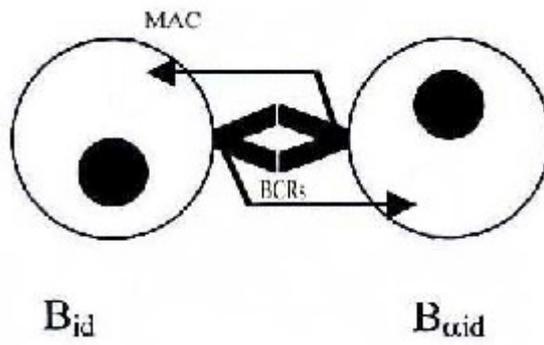
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## Illustrations

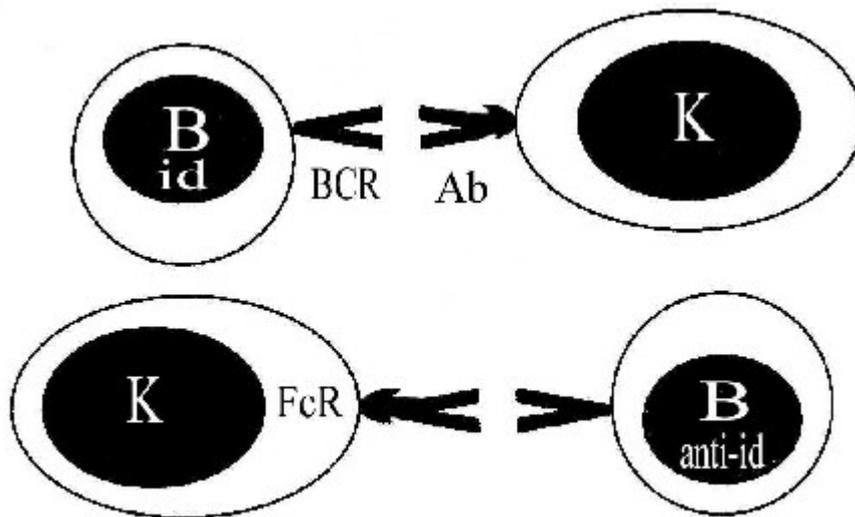
### Illustration 1

Assured Mutual Destruction by complement



### Illustration 2

Assured Mutual Destruction by ADCC



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