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The role of antibodies in the light of the theory of evolution

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Abstract

The phenomenon of facilitation of viral infections by antibodies (ADE antibody dependent enhancement) as well as the resistance of agammaglobulinemia patients to certain viruses are in contradiction with the protective role of antibodies affirmed by classical immunology. This must be compared to the opsonizing antibodies that promote the specific phagocytosis of extra-cellular bacteria. However, questions about the role of antibodies have been raised since the beginning of the history of immunology. More recently, Pierre Sonigo has shed light on the contradictions between the finalist interpretation of the role of lymphocytes and the theory of evolution: how can it be explained that cells are selected to protect the organism they constitute? The role of anti-viral and anti-intracellular bacteria antibodies could be to allow phagocytosis by the cells: either directly by the Fc fragment of immunoglobulins, or via the complement for many cell types. This makes it easy to understand the selection of antibody-secreting cells. Natural selection favors the cells that produce the most affine Ig and thus guides the maturation of the proB cell to the plasma cell. A review of recent publications in theoretical immunology is consistent with this hypothesis. The theory of evolution should be integrated at every level of research and teaching in immunology, as it is for biology as a whole.

Keywords: *Immunology, Evolution, Antibodies, Virology*

1. Introduction

The phenomenon of antibody facilitation of viral infections has recently been re-discussed in relation to the clinical aspect of Covid-19 (Yushun *et al.*, 2020 and Banoun, 2020) and vaccines against this infection (Roper and Rehm, 2009). Antibody dependent enhancement is the accepted mechanism to explain severe reinfections due to dengue virus—among others—(Taylor *et al.*, 2015) as well as the higher occurrence of severe dengue in vaccinated (compared to unvaccinated, Feinberg and Ahmed, 2017).

This effect of antibodies appears to contradict immunological theory, which states that the "role" of antibodies is to protect organisms against pathogens, including viruses.

However, contradictory observations have long been noted.

Already in 1956, a review was published (Good and Zak, 1956) which referred to "*the clinical paradox posed by the apparently satisfactory resistance of patients with agammaglobulinemia to certain viral infections and the failure*

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of their response to the virus antigen.... ". As noted by Burnet (1968), measles immunity is independent of antibodies, but depends solely on cellular immunity. The same demonstration has recently been made for immunity to VSV (*vesicular stomatitis virus*, Moseman *et al.*, 2012).

These observations have been reviewed by Sanna and Burton (2000). They are criticized because all patients diagnosed wuth aγglobulinemia would have received IM immunoglobulin as early as the early 1950s, and thus the complete null phenotype has been little studied. The authors suggest that the treatment given to these patients indicates that antibodies may play a role in viral infections. Some viral infections that these patients developed before treatment virtually disappeared after the initiation of treatment. However, it cannot be denied that the aγglobulinemia patients were discovered by the bacterial infections they developed and not by the viral infections.

It appears that humoral immunity plays a role in HSV (*Herpes simplex virus*, neurologically disseminated enterovirus) infections for viruses with nervous tropism and for persistent viral infections.

Moreover, it is difficult to attribute the discovery of an infection in an antibody deficient patient to a particular virus: the serological diagnosis is inoperative; it was necessary to wait for the culture of the viruses and especially the PCR to affirm a viral infection.

Therefore, this last publication does not call into question the first observations on aγglobulinemia patients: patients are very sensitive to bacterial infections and for the majority of viral infections, their sensitivity is comparable to that of the general population.

Much more recently, the pandemic at Covid-19 has mobilized thousands of researchers and allowed significant advances in immunology and virology. One study compared serologies and cell type immunity in Covid-19 index patients and their contacts: only index patients became seropositive, but both groups showed robust and specific cell type reactivity to SARS-CoV-2 (the virus responsible for Covid-19) (Gallais *et al.*, 2020).

Similarly Sekine *et al.* (2020) showed that most individuals with asymptomatic or moderate Covid-19 generated highly functional durable memory T-cell responses in the absence of a corresponding humoral response.

The role of antibodies in bacterial infections is well established in the defense against extracellular bacterial infections (as opposed to intracellular infections) (Berche, 1988). The frequency of infections in patients with genetic abnormalities of phagocytes is indicative of the importance of phagocytosis.

Bacteria, once phagocytized, are degraded and then exocytosed, making the antigens accessible to the cells of adaptive immunity. The antibodies then act by promoting phagocytosis, which is the natural process of fighting pathogenic bacteria: they are opsonizing antibodies, another term for facilitators. Could the neutralization and agglutination of bacteria observed *in vitro* not occur *in vivo*?

Complement (a group of serum proteins) plays an important role in phagocytosis. These proteins act on the one hand by binding to specific antibodies, but complement is also activated by the alternating pathway induced directly by surface bacterial antigens: lipopolysaccarides, capsule polyosides, lipotechoic acids, and this in the absence of antibodies.

However, as with viral infections, the first line of defense is innate immunity: during a primary infection it takes 7 to 10 days to mount a specific humoral reaction, and it is non-specific phagocytosis that operates first. A good example is pneumococcal pneumonia. Pneumococcus is a commensal upper airway bacterium that becomes pathogenic when it acquires a phagocytosis-resistant capsule. In young adults the evolution is typical: after incubation of 1 to 3 days, a sudden onset, high fever, cough, the evolution is favorable in 8-10 days with a sudden improvement. This improvement corresponds to the appearance of specific antibodies. The inflammatory (polynuclear) reaction aided by the opsonizing specific antibodies will destroy the pneumococci and lead to healing.

How can this opsonizing role of antibacterial antibodies be related to the phenomenon of the facilitation of viral infections by the antibodies?

Pierre Sonigo, one of the discoverers of the AIDS virus in the 1980s, reflected on the theory of immunology and the problems it poses in relation to the theory of evolution (Kupiec and Sonigo, 2003).

Before giving a brief summary of his theses, a historical overview of this science can account for the theoretical gaps that accompanied its birth.

2. History

Immunology is commonly defined as the science that studies the defense systems of living organisms against external aggressions. These systems exist from the origin of life and have evolved of course with it (Rascol *et al.*, 2007).

Immunological science first developed as a simple commentary on vaccination techniques, discovered empirically. Phagocytosis, discovered in 1883, was left aside in favour of the *in vitro* study of humoral immunity - antigen-antibody interaction after chemical purification (Moulin, 1983).

The term immunological "system" is problematic because it implies finalism and invariance, which is already incoherent with Darwinism. We see a system because we attribute to it the role of protecting us. The system would be mature at a certain age in children, and it would be a given until senescence, when it would collapse (Vallet *et al.*, 2019). But immunity refers to both a process and a result: the process is the one by which the organism defends itself against an infectious disease, and the result is the ability to resist reinfection against the same pathogen. The process is in constant evolution in relation to the environment: the immunity of the newborn is built up in relation to the microbiota it encounters at birth. This process is active throughout life in response to the microbiota and external pathogens: it is a co-evolution of the microbiota and the host's 'immune' cells (Pirofski and Casadevall, 2012).

The methodological reductionism essential to the practice of science has led to the distinction between cellular and humoral immunity.

The theory of cellular immunity has long since fallen into the background; the emphasis from the beginning, as mentioned above, has been on serology, which is, moreover, the former name of the specialty in France: the study of soluble factors that can be easily isolated from serum from blood. Nowadays serology has an additional advantage over cellular immunity: it is easily automated and can integrate an industrial process. Conversely, individualized study of cellular immunity for different patients is not yet possible. However, it is now accepted that the two processes are closely intertwined: the cells of the immune system interact with each other through numerous molecules that they secrete and absorb.

Where do the terms antigen and antibody come from?

"*The term antigen appears for the first time in the annals of the Institut Pasteur. It enters everyday language as quickly as the term antibody. The word gene, commonly used at that time by many biologists, did not refer to genetics. It corresponds to the idea that the antigen establishes a relationship with the antibody, or rather modifies it. Moreover, the definition remains very circular, the antigen inducing the antibody and vice versa. One characterizes the other in a perfect tautology: the antibody is the one that recognizes the antigen*"(Debré and Gonzales, 2013). Moreover, the Anglo-Saxons felt the need to invent a false etymology for the term antigen: "antibody generator"! (Wikipedia, 2016).

"*At the time of Behring and Roux, the nature of antibodies was unknown, but their role seemed clear: to defend the body. Then this role was questioned. The complement-fixing antibody is cytotoxic for the attacker and sometimes also for the host. It can facilitate and protect the graft* " (Moulin, 1983).

These questions about the role of antibodies seem to be forgotten nowadays, although they are coming back to the surface of the debate following the "paradoxical" observations of the antibody dependent enhancement.

3. Pierre Sonigo's evolutionary vision

Jean-Jacques Kupiec and Pierre Sonigo propose to refer to the theory of evolution by applying it at the cellular level (Kupiec and Sonigo, 2003):

"*The cells that compose us live for them, not for us. The theory of evolution, which predicts the emergence of equilibria by variation and selection, not by a prior plan, is not applied by biologists at the cellular or molecular level. Immunology is built on a curious mixture of the Darwinian model of random selection (which helps explain antibody synthesis) and specificity in molecular biology. Specificity is a fixist concept that does not fit well with evolution. In this respect immunology is exemplary of the split in modern biology between the theory of evolution and genetic determinism. The theory of clonal selection of antibody synthesis is not compatible with the theory of evolution, although it does contain the alternation of chance and selection.*"

(This is the theory of Jerne (1955), Burnet (1957) Nature (2007), according to which information pre-exists in the cell. The external environment intervenes only at the level of the selection of cell clones, to amplify an

existing response. Tonegawa (1983) explains how recombinations and mutations in lymphocyte genes increase the diversity of variable chains of synthesized immunoglobulins).

"*But selection is conceived as a signal, and the signal is an order, not a selective advantage in itself. The benefit obtained does not benefit the cell but the entire organism: this change in the object of selection is problematic. Natural selection cannot retain a program that is only a virtual, unrealized representation of a function. The lymphocyte that has the best antibody (which attaches best to the antigen) multiplies because it has captured the resources that allow it to do so*" (Kupiec and Sonigo, 2003).

4. About the role of antibodies in viral infections

Let's apply this same reasoning to the "paradoxical" phenomenon of antibody dependent enhancement of viral infections. P Sonigo's remark about AIDS virus research can be applied to the study of antibodies:

"*Descriptions of the virus at the molecular level are becoming more and more detailed. The complexity of the virus is becoming clearer and clearer.... If what we discover is increasingly complex, isn't this progress the opposite of a science that is supposed to shed light and not elaborate on complexity?*" (Kupiec and Sonigo, 2003).

This complexification can be found, for example, in the study of plasma cells (Burjanadze *et al.*, 2009).

Pierre Sonigo brought together the two fields of immunology (humoral and cellular) in his evolutionary vision.

It is a question here of specifying what his demonstration implies, particularly in serology (in the field of humoral immunity).

We can resume the demonstration of P Sonigo by qualifying the antibody (immunoglobulin) as a hook allowing the cell to capture its food, whether it is a soluble or particulate antigen presenting antigens on its surface (bacteria, viruses, ...). Historically, the antigen-antibody interaction has been studied *in vitro*, in a saline environment far from the natural environment inside an organism. Similarly, the interactions of antibodies or viruses with cultured cells are studied in a saline medium (see on this subject Cunchillos, 2014, in the chapter on enzymatic reactions, why the kinetics of the reactions observed *in vitro* cannot be transposed to what happens *in vivo*, and also Kupiec, 2019). "The forces that unite antibodies to haptens are not fundamentally different from those governing the different interactions between proteins or between enzymes and substrates" (Chatenoud and Bach, 2012).

The agglutination power of antibodies to particulate antigens is observed *in vitro*: this power is used in serology to quantify the presence of antibodies in a serum. The ability of certain antibodies to neutralize the activity of a virus or bacterium is also observed *in vitro*. For example, in a culture of virus-sensitive cells, a virus can be prevented from entering the target cells by adding an antibody to the virus in the culture medium.

From this, it was inferred that these antibodies were also agglutinating or neutralizing *in vivo*. Could the neutralization and agglutination observed *in vitro* not occur *in vivo*? From an evolutionary point of view, what would be the "interest" for plasma cells to secrete antibodies to agglutinate or neutralize an antigen or virus? If this interaction is not followed by phagocytosis? How could these plasma cells be selected? If, on the contrary, the antibodies, *in vivo*, do not agglutinate or neutralize anything, but allow the plasma cell to capture the antigen, everything becomes simple! The "role" of the antibody then becomes that of allowing phagocytosis by the cells. The B cell line is the one that gives rise to plasma cells, the "antibody factories" (Batista, 2017). How can this frenzy of immunoglobulin production be explained from an evolutionary point of view other than by the supposed need to protect the organism that harbors them from aggressors?

Immunoglobulins (Ig) are proteins present in membrane form (BCR, B cell receptor) and in soluble form (antibodies): the mere fact that these Ig are named in two different ways depending on whether they are present in membrane form or in soluble form is indicative of the epistemological obstacle to understanding their role. These BCRs are internalized and allow the capture and subsequent digestion of the antigen by the B cell. This is "unexpected" for the authors of one study (taken at random but significant, Pinto *et al.*, 2013). The affinity of this BCR for the antigen obviously plays a key role in the differentiation and proliferation of B cells (Yam-Puc *et al.*, 2018). Yet it has long been known that the Fc fragment of IgG is essential for antibody immunosuppression, although the Fab fragment binds more strongly to the antigen compared to complete IgG (Chan and Sinclair, 1971).

Moreover, it is difficult to find publications highlighting the structure of BCRs according to the stage of B cell differentiation. In particular, scientists are more interested in the non-specific and membrane-bound part (the cytoplasmic tail) of the Ig that makes up the BCR: they seek to identify the signals that would trigger the modification of the B cell's gene expression once it has picked up the antigen on its surface (Xu *et al.*, 2014).

These same scientists are much less interested in the specific Fab part of the antigen and its internalization: how does this capture and digestion of the antigen influence gene expression? They go so far as to be surprised that changes in gene expression profiles are shared between memory B cells, memory T cells and hematopoietic stem cells, suggesting a non-specific mechanism of differentiation under the action of "transcription factors" (Kupiec, 2019). In a figure from a review concerning the regulation of B cell development, the antigen is moreover forgotten: only the antibody produced by the cells is supposed to intervene in the maturation of the lineage (Shapiro-Shelef and Calame, 2005).

It is easy to get lost in the jungle of studies that seek to identify in an increasingly complex manner the intracellular "signals" activated by the internalization of the BCR attached to the antigen; the authors of these publications seem to forget that the BCR is made up of the same Ig that is also secreted by the plasma cell, and that the internalization of the BCR-Ag complex is followed by the digestion of the antigen. However, this information is found in textbooks (Alberts *et al.*, 2002). Yet, as Chomin Cunchillos explains, if the teaching of biology were based on the theory of evolution, it would be so much simpler to explain B cell differentiation and proliferation on this basis!

All Ig classes are represented in BCR, not only IgA and IgM, always obviously according to the stage of differentiation (Xu *et al.*, 2014). The cells of the B lineage are, at all stages of maturation, capable of capturing Ig-Ag complexes and feeding on them. The greater the affinity of the Ig they secrete for Ag, the more efficient the capture of resources and the more they proliferate; natural selection favors the cells that produce the most affine Ig and thus guides the maturation from the proB cell to the plasma cell. If one can translate, all this is clearly stated in publications that try to explain why and how B lineage cells differentiate, mature, proliferate and synthesize large amounts of antigens. It is all in the vocabulary that we just have to change: instead of transformation of the antigen once captured by the cell, we should read digestion, instead of presentation of the antigen on the cell surface, we should read rejection of the waste products of digestion captured by other cells that revel in it :

"*The antigen, the starting resource, is phagocyted and digested by a first kind of immune cells that regurgitate the metabolites resulting from this digestion. Other kinds of cells will feed on this waste. Among these wastes we find what are called cytokines which are the feast of certain cells whose proliferation they allow. Rather than assuming the existence of cascading signals for regulation and metabolism, it is sufficient to consider a single chain of transformation: the binding of the molecule to the cell membrane, its penetration and then the steps of its metabolic treatment in continuity. A cytokine (with non-specific effect) will induce the proliferation of a large population of lymphocytes; an antigen will only influence a small number of very specialized clones*" (Kupiec and Sonigo, 2003).

This metabolic chain expresses the cooperation between cells (another constant of biological evolution that Darwin insisted on): cells stabilize in a given type according to the interactions they can establish with their environment; they are able to use in an optimal way the available resources, whether, here, native antigens or the waste products of the digestion of antigens by other cells (Kupiec, 2019).

How do memory plasma cells feed when there is no more antigen? They take refuge in places where non-specific "growth factors" are quite abundant: in the bone marrow germination centers (Farhi, 1989) (we humans also enjoy this nutrient-rich bone marrow!). These growth factors are naturally food for cells of all kinds.

But the countless antigens that an organism encounters are nutrients that many cell types covet. There is intense competition for immunoglobulin-fixed antigens, not only between plasma cell lines but also with other cell types.

Plasma cells, NK cells, macrophages and many other less "specialized" cells have receptors for the Fc fragment of immunoglobulins (this fragment is the non-specific part of the molecule that does not bind to the antigen). I will not discuss here the term "receptor" and what it implies about the specificity of molecular interactions (Kupiec, 2019; and Cunchillos, 2014). This "receptor" is a protein that interacts preferentially with Ig Fc and then allows the internalization of the Ig-Ag complex that will be digested by the cell. As mentioned above, many immune cells have Fc receptors, but for many cell types there is another way to capture this resource: complement fixation. Complement is a set of proteins, the main one being C1Q, which has a high

affinity for the Fc fragment of Ig. Endothelial cells, fibroblasts, among others, possess receptors for this C1Q and are capable of capturing antigens by this means (Fonseca *et al.*, 2001). It has been shown that this pathway facilitates certain viral infections (for the Ebola virus, for some Parvoviruses, Von Kietzell *et al.*, 2014).

These FcRs play an important role in facilitating non-viral infections in autoimmune diseases. For tumors, this FcR may have a role in reducing metastasis by anti-tumor antibodies (Ravetch and Bolland, 2001). Conversely, the immunological facilitation of tumors could be interpreted in the same way. When mice are immunized against the antigens of their tumors, tumors may develop faster in immunized animals (Vivier and Daëron, 2018): are tumor cells able to capture antibodies directed against their surface antigens, these antibodies then becoming their food, which explains their proliferation?

Despite the lack of purpose of their production, antibodies can however play a protective role in viral reinfections and are necessary for defense against extracellular bacterial infections: it should therefore be explained why antibody facilitation is not always observed in viral infections. It has obviously not been researched, but it has sometimes been imposed because it is too visible, as in the case of influenza, dengue fever or coronavirus infections (a complete review has been published on antibody facilitation of viral infections, Taylor *et al.*, 2015).

It can be assumed that, in general, innate antiviral immunity eliminates most attackers before antibodies are synthesized sufficiently to facilitate infection (Fafi-Kremer, 2020). It has recently been shown that immunity to VSV (*vesicular stomatitis virus*) is independent of antibodies, but depends solely on cellular immunity. B lymphocytes are thought to play a non-specific role in stimulating T cells: they secrete a "lymphotoxin" capable of activating macrophages, which then become capable of secreting Interferon 1; this "lymphotoxin" can be interpreted as food for the macrophage and is thought to induce its proliferation.

The quantity and affinity of the antibodies produced are important to consider. Soluble antibodies secreted in excess by plasma cells represent a nutritive resource for many cell types that could capture them before they can induce facilitation. Indeed this facilitation occurs for certain serum antibody levels and for low affinity antibodies, so not in all circumstances: this has been shown for dengue re-infections (Katzelnick *et al.*, 2017).

There is no question here of delving into the details of Pierre Sonigo's vision, this time applying it to adaptive cellular immunity: it would be interesting to investigate the role of competition between cells for the capture of antigenic resources. T Cell Receptors (TCR) are in fact also membrane immunoglobulins and are "encoded" by genes similar to those that code for antibodies (Britannica *et al.*, 2020). They recognize antigenic fragments of pathogens partially digested by infected cells: these fragments could be interpreted as waste products rejected by these cells.

In a review, Kaspenberg (2003) underlines the role of the antigen dose and the affinity of TCR receptors for it in the orientation of T cell differentiation (towards the Th1, Th2, Treg pathways): competition between cells for the nutrient resource would be the key to differentiation and proliferation.

5. Conclusion

Antibodies play a central role in the fight against extracellular bacterial infections and may play a significant role in viral reinfections. Conversely, in intracellular viral and bacterial infections their role may be limited to facilitating infection. A common characteristic of intracellular viruses and bacteria is that they divide within the cell, unlike extracellular bacteria.

During bacterial membrane synthesis and division, it can be assumed that the accessibility of bacterial membrane antigens is modified. Antibodies could be secreted in large quantities and with a strong affinity only against the antigens of extracellular bacteria: bacterial division in the extracellular medium would release a large quantity of bacterial antigens capable of proliferating increasingly specific plasma cells. The antigens of intracellular bacteria would be excreted only after division in the cell and antibodies directed against them would not be able to hinder bacterial division. Antibodies would play a protective role only against extracellular bacteria because they would act at the time of division, when antigens are more accessible and in greater quantity.

Concerning viral infections, the recent Covid epidemic has led to advances in the understanding of the role of antibodies. They are often not synthesized in benign or asymptomatic infections (Gallais *et al.*, 2020), when cellular immunity is activated. It is therefore possible that, as suggested by the authors and also by another study on the cellular T response to Covid (Le Bert *et al.*, 2020), the innate response may abort full viral replication,

as the small amount of accessible viral antigens is not sufficient to induce a humoral response. However, the low level of viral replication in these poorly or asymptomatically active patients would be sufficient to activate a robust cellular response. The role of antibodies in Covid-19 has been evoked in the immunopathological phenomena characteristic of this disease (Banoun, 2020): severe infections are associated with high antibody levels compared to those of moderate infections.

With regard to bacterial infections, the phenomenon of immune tolerance should be tested by the theory of evolution. Indeed, most extracellular pathogenic bacteria are commensal bacteria that become pathogenic under certain circumstances (modification of the flora, mucous membranes, immune status of the carrier, ...): in normal times they do not cause infection, do they cause the synthesis of antibodies directed against them?

If so, why do these antibodies not act?

If not, this phenomenon of immune tolerance can be explained by the formation of the immune system according to the microbiota that develops at birth. Classically, the apoptosis of lymphocytes reactive to "self" antigens and commensal bacteria is used to explain this tolerance. Apoptosis is not compatible with the theory of evolution: how would cells that "commit suicide" be selected? The mechanism by which negative selection can lead to the elimination of B cells that react to autoantigens is not elucidated (clonal deletion or receptor editing) (Nemazee, 2017).

According to Eric Vivier, professor of immunology, "The immune response is always induced by a discontinuity that is not only qualitative. The important thing is change and its rapidity. What makes an antigen is a variation in quality over time and a difference in quantity. The microbial world controls our immune system as much as the opposite" (Vivier and Daëron, 2018).

Is it possible to reinterpret the work of thousands of researchers and the results of thousands of publications?

How can immunology research be reoriented in an evolutionary direction?

Is it possible to abandon the idea that antibodies do not always have a protective role, but that in certain cases (acute viral infections, intracellular bacterial infections) they are simple witnesses of an encounter with a pathogen?

How can the theory of evolution be integrated at each level of biology teaching and not just as a separate field? Teaching immunology starting with the immune defenses of the first organisms (bacteria) could make this science easier to explain: innate immunity may have preceded adaptive immunity and should therefore be mentioned first (Tsakou-Ngouafo *et al.*, 2020): "A complex innate immune system may have existed long before the emergence of the vertebrate ancestor. This may have included large multigene families able to recognize foreign pathogens, cell proliferation and immune memory following pathogen contact…. ". Pathogen recognition is believed to be mediated by non-specific receptors capable of binding to the PAMP (Pathogen-associated molecular pattern) motifs of pathogens.

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