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(Note: It is an annoyance that I cannot cite this work. If there is anyone out there who would be prepared to let it have a place in a citable journal, I would be most grateful for this.)

Opinion

Flushing out the phlogiston? (Restructuring of the "immune system").

Keywords: Animal; Apoptosis; Cell Communication; Complement; Evolution; Gap Junctions; Homeostasis; Human; Hypothesis; Immunologic Surveillance; Immunity, Natural; Models, Biological; Models, Immunological; Necrosis; Phagocytes; Self Tolerance

Abstract

Huge advances have been made in unravelling the detailed interactions of immune cells and their products. Nevertheless, there is still fierce debate and difference of opinion about the grand plan - the logical structure - of the 'immune system'. The reason may be that an 'immune system' (a foreign organism seeking system) is just as illusory and non-existent as phlogiston. In a series of articles, I have progressively moved to the conclusion that the system is not an 'immune' but a 'morphostatic' (tissue homeostatic) system. This article tidies up the concept and explores further ramifications of the principle.

Quotations

'Nothing in biology makes sense except in the light of evolution' – T. Dobzhansky, 1977

"Immunology is an invention of the devil, who is making it up as he goes along because he's not too clear about this stuff either." . . . "Besides, immunology is what we North Americans call a Rube Goldberg system, referring to old cartoons about how to turn on the light, for example: you trip over a footstool, thus startling the cat, who bumps into the kitchen door, which swings shut, knocking over a chair that hits the light switch . . . you get the idea. There has to be an easier way." – Janice H Tanne, 1990

Introduction

In metazoans, the first 'immune' cell to evolve was the phagocyte. This cell clears away the 'mess' that accumulates within each colony of cells that constitutes an animal (the zygote derived colony). It also encourages the regeneration of lost tissues. It is a general assumption that vertebrates have evolved an immune system that is 'designed' to identify and eliminate foreign organisms.

Now, whilst invading, foreign organisms are undoubtedly a major threat to morphostasis, we need to remember three things. First, the tissue debris that accumulates from degenerating cells is an essential resource for pathogenic organisms. A prime strategy for the morphostatic system is to operate a "scorched earth" policy (an impeccably clean extracellular environment) to deny foreign organisms a suitable substrate for growth and reproduction. Second, pathogenic organisms need to create extra- or intra-cellular debris to satisfy this need for a substrate. A substantial part of a pathogenic organism's genome is dedicated to this role and this probably leads to its reduced survivability in a saprophyte's preferred environment. Third, dedicated, intracellular, pathogenic organisms need to get themselves invited in and it seems likely that the provocative display of so called PAMPs (pathogen associated molecular patterns) might be one of their chosen (Trojan-horse-style) strategies.

So, it may be possible to restructure our perception of immune cell function so that it now champions 'the clearance of tissue mess' as the real *raison d'être* - the grand plan - of the system. By this view, foreign organisms are only noticed because they appear to the system as mess or they provoke a tissue mess that triggers clearance. If this perspective is valid then it would no longer be justified to regard, as heresy, the counterintuitive assertion that "there is no such thing as an immune system". It might even show us some

shortcuts to establish what each element of the system has evolved to do. The provocative title of this article implies that we may be witnessing a conceptual-Jack-in-the-Box that will trigger an unfolding revolution in our understanding of immune function.

This article condenses and extends concepts from previous papers (Cunliffe, 1995, 1997, 1998, 1999) into a synopsis so new references are kept to a minimum. It is dominantly theoretical so readers must decide, for themselves, which conjectures are valid and which are flawed.

The evolution of morphostasis

- Let us look at the sequence of 'shells' that eventually form the mammalian 'immune system' (Cunliffe, 1995, 1997). All the shells remain fully functional and continue to fulfil their original purposes. None are abandoned. They are layered around each other like the layers of a Russian doll. They are also used in the same sequence - the inner layers first. Each layer will either manage or fail to resolve the problem. Failure to resolve the problem will promote the response to move out to the next shell. These form a barrage of defence lines to counter mess. When a defence line fails, the system retrenches to the next line of defence.
- In the beginning, heat shock proteins identify - then attempt to repair - protein trash; ubiquitins escort terminally malformed proteins off the premises; endosomes chop them up into short peptides.
- Elective suicide (a forerunner of apoptosis) evolves as a mechanism to limit the spread of rampant disease through a colony. A similar strategy is even used in colonial bacteria.
- Cell adhesion molecules (CAMs), surface associated molecules and intercellular junctions evolve. These give cells a sense of 'belonging-to-the-colony' and **this** enables them to dock with one **another**. This is a discrimination of self from non-self. It remains the fundamental root of 'self'-'non-self' discrimination in mammals.
- Homeotic genes allow cells to adopt alternative (cellular) body plans. When gap junctions evolved (about 700my ago), they (somehow) enabled alternative, homeotic body plans to expand their sphere of influence to cover blocks of cells interconnected by bridges of cytoplasm - so enlarging the body plan. It also enabled the simultaneous use of several body plans within the zygote derived colony.
- A primitive metazoan will require the following of its component cells: when the well being of a cell is compromised it will be expected to detach itself from the colony and it may be extruded from its immediate grouping. It may re-attach provided it fixes the damage. If not, it will be expected to do the decent thing, sanitise its contents (by trashing them) and then invite its own gentle absorption by surrounding cells. Lost cells will be replaced through cell replication. Individual cells are expected to monitor and maintain their own health. If they cannot identify that they are malfunctioning, and so go on to spill their cytoplasm, then they can expect no mercy from the surrounding colonial (self) cells. Such sick cells are potentially dangerous. They will be aggressively attacked by dedicated phagocytes and cleared away together with their spilled contents.
- What has changed in mammals? Nothing - not, at least, as far as the grand plan is concerned; but the system has since been elaborated to enhance the intracellular destruction of suspect cells. It does so by encouraging particular cells - those that sport a caricature resembling cells that spilled their contents on a previous occasion - to adopt a lowered threshold to apoptosis.
- Phagocytes pay little attention to cells that are in junctional communication with each other. These cells are stable and healthy. Phagocytes concentrate their attention on the suspicious group that have detached themselves or that were never attached in the first place (interlopers). They use a docking system to attach their uropod to an underlying block of communicating cells. They (probably) check, with their lamellipods, that adjacent cells are in (pulsatile?) ionic continuity. This docking by the uropod has low specificity. It is able to attach to allogeneic and even xenogeneic cells. Dedicated pathogens may find ways of fooling this surveillance.
- Natural killer-(NK)-like cells evolve as an extension of this low-specificity recognition. Using CAMs already evolved to enhance 'neural' interconnections (probably IgSFs, N-CAM-like), they learn to enhance recognition of detached cells so that this becomes more specific to the individual. By hanging representative peptides off the cell surface, in association with an N-CAM-like molecule (Mhc class I like), local accumulations of these cells can sense when there is a significant deviation away from a healthy-self, Mhc+peptide signature. The pleomorphism of this identity system and its germline receptor mechanism (possibly enhanced by RNA splicing) can gradually expand from two to numerous different specificities. Possession of selfness ensures that a cell will not be attacked; its absence or loss ensures that it will. This system is adept at recognising the internal cell turmoil stirred up

by successful Trojan-horse invaders. Should any detached cells still go on to lysis, the next stage will be invoked. Note that Tc cell activity is a functional inversion of this NK-like activity.

- Tc-like cells can now evolve. Detached cells that die by apoptosis have proven that they are able to deal with whatever caused their malfunction. ClassI+peptide epitopes hung off the cell's surface allows the respective Tc-cell receptor to get a snapshot of the turmoil that is going on in the cytoplasm of that sick cell. Cells that sport a caricature, similar to cells that previously died by apoptosis, can be safely left to get on with it by themselves; but cells resembling those that spilled their cytoplasmic contents last time round have proven that they cannot. On any new encounter, they need to be recognised and encouraged into an early apoptosis.
- A key point to grasp is that it matters not one jot whether the Mhc+peptide signature is formed dominantly from peptides derived from self or from some foreign intracellular nasty. A precursor Tc cell that is able to recognise this combinatorial epitope will classify the encounter according to an association with tidy (apoptotic) or messy (leaky) death. A previous encounter in a generally messy environment will encourage an aggressive response in the future. Paratopes interacting with Mhc+self-peptide are relatively resistant to an easy promotion into aggression. The staggeringly enormous volume of successful apoptosis that occurs naturally in the body mops up precursor T- cells, capable of responding to the presented epitopes, into tolerance. There is also a tendency for younger, precursor Tc cells to be hard to enrol into aggression. Tc cells are designed to kill self-cells. This is their cardinal role. That is why it is so easy to produce adjuvant arthritis and other experimental autoimmune disorders (note that over-exuberant Th1 aggression is a dominant accompaniment of most of these disorders). They are precipitated when there is a great deal of membrane damage, cytoplasmic spillage and a prolonged stimulation of the aggressive T-cell system but there is an absence (or paucity) of clearly strange antigen to focus attention onto the disordered cells that provoked the mess. By rapidly focusing aggressive attention on the cells that are rupturing (say eg, due to a viral infection) then the whole process can be brought to a rapid resolution as this selective aggression will be directed preferentially towards some unusual epitope characteristic of the infected cells. Since there will be only a few precursor Tc cells available that are specific to the local tissue (most having been mopped up following previous apoptosis) and they are, anyway, young and resistant to recruitment into aggression, the differential expansion of aggressive Tc cell clones will strongly favour strange over self epitopes. Note that macrophages that die catastrophically, rather than in a controlled shutdown (apoptosis), should also stimulate Tc cells.
- Cells that die suddenly in trauma (e.g. heart attacks, burns) have not been preparing for apoptosis. Cells that die of viral infections or other intracellular nasties have probably moved somewhere along the path towards it. This means that cells that die by trauma do not spill much Il-1 whereas infected cells do. Spilt Il-1 is a strong contender to be one of the danger signals (eicosanoids, which are released after membrane perturbations, are another). (Note that apoptotic bodies that rupture before they are cleared should be a potent trigger of T-cell aggression.) Nevertheless, Dressler's syndrome is the occasional autoimmune sequel to a heart attack - so trauma does increase the risk of autoimmunity. Similarly, in burns and major trauma, autoimmune activity is easy to demonstrate. Indeed, it is the probable precipitant of the phagocytic anergy that appears before multiple organ failure sets in. Any system that allows auto-rejection of normal cells must sport a failsafe cut off device to inhibit the piecemeal destruction of self (Regan and Barbul, 1989).
- (A lot of this paragraph needs to be updated. I am both unsure of why I stated this in this way and embarrassed by it!! I have added an updated, bulleted, paragraph after this one) Th1 cells evolve as an elaboration of the Tc cell system. Now, the cellular and cytoplasmic debris of leaking cells can be digested by APCs and then processed so that representative peptides can be presented on the APC's surface. Apoptosis of these APCs (which have successfully cleared the debris and have detached from the tissues to migrate to and apoptose in the local lymph nodes) will favour tolerance to ClassII+peptide epitopes. But, when these APCs fail to contain the problem, they will start to rupture (together with tissue cells) and create a messy environment that favours Th1 aggression. On any future encounter with a similarly caricatured APC (not of the pathogen nor of its native antigen), the inflammatory response can be quickly ramped up - bringing in copious aggressive phagocytes and NK cells. This is designed to give inflammation a memory. The newly immigrant phagocytes still have to sort healthy-self-cells from the rest but they are now stirred up into a frenzy of eagerness to get on with this job.
- Th1 cells evolve as an elaboration of the Tc cell system. Now, the cellular and cytoplasmic debris of leaking cells can be ingested by APCs and then processed so that representative peptides can be presented on the APC's surface. They detach from the tissues and migrate to the local lymph nodes. There they trigger appropriate naïve T-cells and commit them to either tolerance or aggression, according to the inflammatory milieu in which they met their

debris. On any future encounter with a similarly caricatured APC (not of the pathogen nor of its native antigen), the inflammatory response can be quickly ramped up (aggression) or dampened (tolerance) - bringing in copious aggressive phagocytes and NK cells. This results in giving inflammation a memory. The newly immigrant phagocytes still have to sort healthy-self-cells from the rest but they are now stirred up into a frenzy of eagerness to get on with this job.

- Since extensive tissue destruction is undesirable, phagocytes must be inhibited when the Th1 cell amplification process becomes too fierce. Phagocyte activity is consequently inhibited (as, eg in a boil) and this increases the amount of debris left to be cleaned up; the IgM antibody system arose to act as a debris mop. B-cells (cells that evolve from the macrophage line) have an immunoglobulin receptor that internalises only targeted debris and processes this into peptide+ClassII epitopes. Then, when a suitable CD4 T-cell receptor encounters this epitope, it triggers the respective B-cell to differentiate into a plasma cell that then secretes free antibodies (but note that some IgM production is independent of T-cell help). This then tags the debris and enhances its clearance. So, progression to Th2 activity is most likely to occur when cell-mediated auto-rejection is inhibited in the interests of inhibiting piecemeal self-destruction. But this inhibits the clean disposal of mess. The release of IgM is an attempt to compensate for this. All the other immunoglobulins have evolved as shells that envelop IgM (e.g. IgG, IgA, IgE).
- Thymic tolerance is probably designed to enhance the tolerance of lymphocytes (perhaps macrophages and epithelial cells too) so that it pre-emptively inhibits their auto-rejection. These cells are expected to migrate to lymph nodes - areas where mess-making agents are likely to be concentrated. This is probably why the thymus turned up in the pharyngeal arch - close to the place where copious seawater (with many mess making contaminants) is passed across the large and convoluted surfaces of the gills. In this view, both thymic and peripheral tolerance are seen as the consequence of the tidy disposal of apoptotic cells and are essentially the same process.

Synopsis

So, the whole process works through differential rates of cell death. Irremediably dysfunctional cells are expected to do the decent thing and die early by trashing their cytoplasm. In the process, they sanitise their contents. The fact that infection is a frequent cause of intracellular dysfunction is of no interest to the system. Cells don't think 'I am - or you are - infected'. They realise 'I am - or you are - irrecoverably sick'. The corollary is that there is a differential nurturing of healthy-self-cells that are in junctional communication with their neighbours. The adaptive 'immune system' simply remembers some caricature of those cells (or their debris) that failed to do the decent thing last time and it then watches out for similarly caricatured cells (and their debris) the next time round.

The progression of morphostasis

This leads to some thoughts on how the morphostatic response begins at the innermost shell and progressively enrolls successive shells until morphostasis is achieved. The heat shock protein system may achieve morphostasis on its own, fixing the problem with minimal disruption. When the volume of malformed protein is too great the next stage is induced (eg, the dumping of representative peptides on the cell surface in association with Mhc molecules). Intracellular surveillance watches for cell dysfunction and triggers apoptosis where appropriate. Where the mess is dominantly genetic, a healthy p53 gene is required in order to trigger apoptosis. Resident phagocytes (dendritic cells) try to remove the debris of cells or organisms that start making a mess (including p53 mutated cells) - and they are mostly successful. But this can fail. So, at this point, the agent that precipitated the crisis has overcome all the defence lines thus far. Now there is an increased flow of lymph bringing in phagocytes from the blood. These will ingest the mess then proceed to apoptosis. They may do this locally or after being swept away in the lymph to the local lymph nodes. When this shell fails to resolve the mess, NK cells are brought into play. These are more specific about self-identity. They concentrate dominantly on disconnected cells. Nevertheless, some mess makers still lead to the rupture of cytoplasm. By this time the lymph flow has increased to a torrent and both immune and detached sick cells are swept off to the local nodes. Now the Tc cell system is brought into play. This memorises the caricature of cells that were associated with cell rupture the last time that they were met. Their first encounter with uncommitted T-cells is in the local lymph nodes. The Tc cell system encourages cells - with a caricature that resembles cells that previously presented in association with rupture - to do the decent thing next time around. This system provides a clean clearance of the sick cells - while it works. But, even this may be overcome - at which time we are left with a mess of spilled cell debris. This debris is easily recognised and eliminated (by phagocytes). The Th1 system then categorises the resulting ClassII+debris-peptide epitope on the basis of whether or not it has previously

been encountered in an inflammatory environment. Aggression (Th1 activity) is favoured when APCs meet the epitope in an inflammatory encounter and Tc activity will be provoked to macrophages that rupture rather than apoptose. When a Th1 cell meets a similarly caricatured phagocyte (which must already have started to clean up the cell debris to be able to sport this epitope on its cell membrane) then it will bring in a whole army of activated phagocytes to carry out the job more swiftly. But this lays the system open to phagocyte anergy. When the going gets too intense, extensive tissue destruction must be aborted by phagocyte anergy - and this results in a failure to contain mess by Th1 induced clearance. This anergy leads to a sea of extracellular debris and so to the need to recruit IgM. I am sure that a little thought would allow us to extend into the next rounds (the other Igs) but I will stop here. I have omitted complement here for brevity - that is covered in the other articles (Cunliffe, 1995, 1997). It is worth noting, though, that complement is also likely to fit better into a 'mess'-non-mess' discriminating system (see below).

Thus, for each insult, there is a sequential move from the inner to the outer shells. Now this is rather like the evolutionary steps that formed the mammalian morphostatic system. Remember that ontogeny tends to shadow phylogeny. So, is the gradual aging of the 'immune system' the stochastic accumulation of all possible responses to various mess-making insults through these shells? For some insults, the move to the outer shells is early and for others it is late. Could this, superimposed by the gradual genetic divergence of the zygote-derived colony, be the source of the immune changes observed as mammals age?

The immune system is dead: long live the immune system

The term immune (freedom from burden or taxes) is now encumbered with the presumption that the system is "designed" to find, identify and kill foreign invaders. This pervasive conviction may be so misleading that we will have to exorcise it - at least for a generation - until we have shed a (mis)conceptual mill-stone. This counterintuitive view must seem strange to those who know that it is manifestly obvious that the system is designed to kill micro-organisms. After all, infection runs rife when the system fails.

And the earth is flat too! Thinking the unthinkable has often been the vanguard to a revolution in understanding. It does not make the old views "wrong" - it simply shows that they did not run deep enough. In particular, such revolutions expose the underlying (false) presumptions.

A heretic idea can be justified by demonstrating that it cannot be dismissed as invalid. While this does not necessarily prove the old view wrong, it helps to expose the hidden assumption. Morphostasis provides an alternative view (Cunliffe, 1998, 1999). It restructures our perspective of a "self/non-self" discriminating system into an "order/disorder" discriminating system. The fundamental principle of life - its *raison d'être* - may be to beat back the tide of entropy. Thus, maintenance and extension of order may be the core function of life. The natural gradient is towards disorder. Living systems use a selfish survival strategy to "rob Peter of a little bit more than they are prepared to pay Paul" to maintain form (molecules through to animals). Selfish is misleading, for there is no persistence without survival. Only the most pervasive, invasive and successful ordering strategies have survived from life's origins. Little wonder, then, that the analogue, catalytic systems that first propagated order were soon themselves ordered by a digitised copy code of tRNA. This began to ensure the faithful propagation, replication and dispersion of order-out-of-the-jaws-of-degeneration systems (in line with "integrity", Dembic, 2000).

By analogy, the immune system is like a mindless caretaker. Unless residents are stood in rows, "holding hands", co-operating and behaving modestly he will ask them for some form of identification. Should they start making a mess - particularly spilling their own or other's innards or disrupting the (connective tissue) structure of the building - then the caretaker will regard them either as potential mess-makers or as mess in need of clearance. To make the system favour its own kind (healthy zygote derived cells) and not some other's, cells will also need to commit tidy suicide by wrapping up their own debris in suitable containers marked "for tidy and quiet disposal" when they become irretrievably compromised. The illusion that non-self organisms are actively hunted is, overwhelmingly, a consequence of the active protection of healthy-self cells in an environment that is otherwise inclined to encourage the degeneration of all cellular material. This leads to the nurture of order and the repulsion of anything potentially disordering. Complement starts the process by coating all biological surfaces with C3 products. Healthy-self cells are protected because their

activated C3 is converted to a C3 derivative that does not attract aggressive phagocyte attention (it might even promote cell-to-cell co-operation).

By this view, anything disordered - self or foreign - is a legitimate target for phagocytes and the retinue of cells that evolved from them and are still commanded by them. The innate and adaptive immune systems cease to be viewed as fundamentally disparate entities.

Gallucci et al (1999) have recently provided compelling evidence that tidy apoptosis leads to T-cell tolerance. This occurs in both the thymus and in the periphery so the two mechanisms are likely to be similar. T-cell aggression probably occurs when controlled shutdown (by apoptosis) is threatened, fails or the volume of apoptosis exceeds the capacity of the surrounding cells and phagocytes to clear it. Apoptotic bodies are potential "inflammatory bombs" that will explode if their membranes burst. The recent demonstration that gap junctions play a critical and unforeseen role in immune cell activation (Oviedo-Orta et al, 2000) adds more weight to the order/disorder perspective.

The finale

An established paradigm can accumulate a large surfeit of apparent anomalies and yet still survive as the valid framework for a majority of minds. A new paradigm must face every apparent anomaly as if it were solid evidence of falsification. To approach omniscience (understanding every facet of how it works and every extrapolation of its function) will require multiple minds and many years of consideration. So, any new paradigm should be assessed on its broad - not its focused - applicability as such omniscience will take years and many protagonists to establish.

Acknowledgements

My thanks to the Wessex Medical Library who made this study possible. Especial thanks to [Jim Trosko](#) for reminding me of phlogiston. I apologise to all those who have reported seminal work that I have either not found or not quoted in this series of articles.

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(Please note that there are many relevant references in the first four articles; I have not repeated them here).

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[Last edited 1st December 2004]

Minor correction/alterations made after 2004 (NOT major revisions) are marked in red. Also!! the title addition to make the content clearer