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Morphostasis and Immunity

Abstract

Scientists have traditionally been resistant to fundamental changes in perspective. New ideas are rejected if they challenge essential, accepted paradigms *(1)*. Here I present a concept that, I believe, represents a paradigm shift in the way self/non-self discrimination is perceived. Traditional opinion has it that lymphocytes carry out this discrimination. I propose an alternative view. Self/non-self discrimination is driven by mechanisms closely related to those that lead to cell sorting in disaggregated embryos. Lymphocytes are only used to classify cells according to their mode of death (apoptosis or necrosis). The hypothesis outlines the process of morphostasis (tissue homeostasis). It fills in much detail about the gradual evolution of the mammalian immune system. Earlier versions of this hypothesis have been reflexly rejected by numerous journals. Until recently, I too was unsure of the validity of the core concept. Recent publications have dispelled this doubt from my mind. A paradigm shift is due.

Abbreviations

HS	healthy self
OTHS	other than healthy self
UHS	unhealthy self
CAM	cell adhesion molecule
GJ	gap junction
ICJ	intercellular junction
SAM	surface associated molecule
IgSF	immunoglobulin superfamily
N-CAM	neural cell adhesion molecule

Introduction

In 1963 the Lancet published a hypothesis, "The role of lymphoid tissue in morphostasis" *(2)*. In this article Burwell made the comment that "immunology still awaits incorporating into the general pattern of biology" and suggested that immune function had an important role to play in morphostasis. Morphostasis is defined as the "steady state condition that maintains a particular (tissue) pattern". It seems to me that immunology is still perceived as a discrete and sharply demarcated system. In this article I hope to persuade you that the origin and continuing drive of immune function is morphostasis and this is the cornerstone of metazoan existence. I contend that the hypothesis is consistent with established observations. The following points set the scene. A morphostatic system must interface with these biological systems:

- Intracellular and molecular biology
- Cell to cell communication and co-operation (gap junctions in particular)
- Embryo
    - development from zygote to mature animal
    - evolution from simple metazoans to mammals
- The general scheme of morphostasis including
    - the surveillance for sick cells
    - cell and animal senescence *(3)*
    - malignancy

    - the changing susceptibility to various diseases with aging
    - the renewal of sick cells and tissues
- Basic pathological mechanisms
- Immunity
    - innate
    - anamnestic
    - immune ontogeny
    - immune phylogeny (from simple metazoans to mammals) *(4)*
    - it should also highlight how metazoan homeostasis and defence diverged as plants split from animals *(5-7)*

Brevity demands a synoptic style so I shall not explore the rationale for proposing a new perspective. What follows is my perception of the process. Its elements are not necessarily statements of accepted fact. The bibliography is chosen to provide an investigative trail: many of the articles provide relevant references.

The zygote derived colony (ZDC)

Every animal consists of a colony derived from a single cell, the zygote. No cell in the ZDC has capabilities that are not potentially present in the zygote's genes or cytoplasm. Each ZDC cell needs some way of preferring its own kind as neighbours and inhibiting the growth of foreign cells or organisms in its vicinity. This is helped by using selective CAMs. These lead to the construction of ICJs, a scaffold of connective tissues and the establishment of electrical/metabolic synchronisation *(8,9)*.

The sophistication of single cells: the self aware cell

Each animal cell is a self assessing unit, able to survey its own behaviour and function. It does this both internally and with regard to its interaction with its neighbours. The cell has a variety of internal checkpoint controls. These are particularly well defined in the growth cycle. When an animal cell malfunctions, it senses the abnormality and notifies other cells that something has gone wrong (by various cytokines, alterations in cell surface markers and by breaking junctional communication). A sick cell may elect to sacrifice itself by apoptosis *(10-12)*: its calcium level rises, it rounds up and its GJs are closed before these and other ICJs are disassembled. Apoptotic cells are phagocytosed by adjacent cells or phagocytes before their membranes burst. ICJs promote cell survival.

HS (cell) / OTHS(cell) discrimination

All metazoan animals are able to make this discrimination. What differs from organism to organism is the sophistication with which it is embellished. It reaches a high level of sophistication in mammals. Every embellishment of the morphostatic system, including anamnestic immunity, revolves around the principle that UHS cells "advertise" their presence.

Morphostasis

Tissue homeostasis is maintained by:

- displaying "flags" on the membranes of HS cells that mark them as HS.
- recognising OTHS cells on the basis of absent HS markers and/or present UHS markers.
- attacking and removing OTHS cells (UHS and foreign cells/organisms).
- replacing lost UHS cells with fresh HS cells (resurgent morphogenesis).

In summary

- **Identity** - healthy ZDC cells display identity markers (these double up as "docking" molecules that lead to ICJs and a connective tissue scaffolding).
- **Self surveillance** - cells are able to sense UHS status.
- **Altruism** - cells are able to opt for suicide (apoptosis).

- **Neighbour surveillance** - cells are able to sense a neighbour's appropriateness. Sick cells either declare their own presence or are recognised as such by their neighbours. These include damaged cells, dying cells, aging cells, genetically damaged cells, ectopic cells, malignant cells, infected cells and other sick cells.

Gap junctions

The cytoplasms of most static cell populations are joined through GJs *(13)*. These channels are shut down when a cell becomes sick (14-17). GJs close as intracellular calcium rises *(13)*. GJ channels are then disassembled during apoptosis. The whole embryo is electrically connected through GJs and this establishes the boundaries of self *(18)*. Within this electrically continuous self there are sub-compartments in which member cells are joined by plaques of GJs that have heightened permeability. They are bordered by a layer of cells that have GJs of lower permeability. These define the compartment borders and they correspond with developmental compartments. N-CAM promotes the construction of highly permeable GJ plaques *(19)*. Three possible explanations for this spring to mind: these plaques contain more GJs; the component GJs are bigger; construction is more efficient and there is a higher yield of good junctions. I propose that the consensus sequence motif of N-CAM, that resembles the Ig constant region, is able to spawn multiple, highly permeable GJs much as the complement C2,C1,C4,C3 cascade spawns multiple well formed MACs around Ig constant regions. If so, the C7,8,9 genes have either evolved from connexon genes or they have highjacked the mechanism that encourages the construction of highly permeable channels, inverting it into an attack mechanism. Note these points: (a) C9 inserts itself into membranes without C3-C8 amplification but this is inefficient; (b) leaky holes lead to a rise in intracellular calcium and so close GJ channels; (c) note the connective tissue structure of C1q.

Apoptosis, necrosis and inflammation

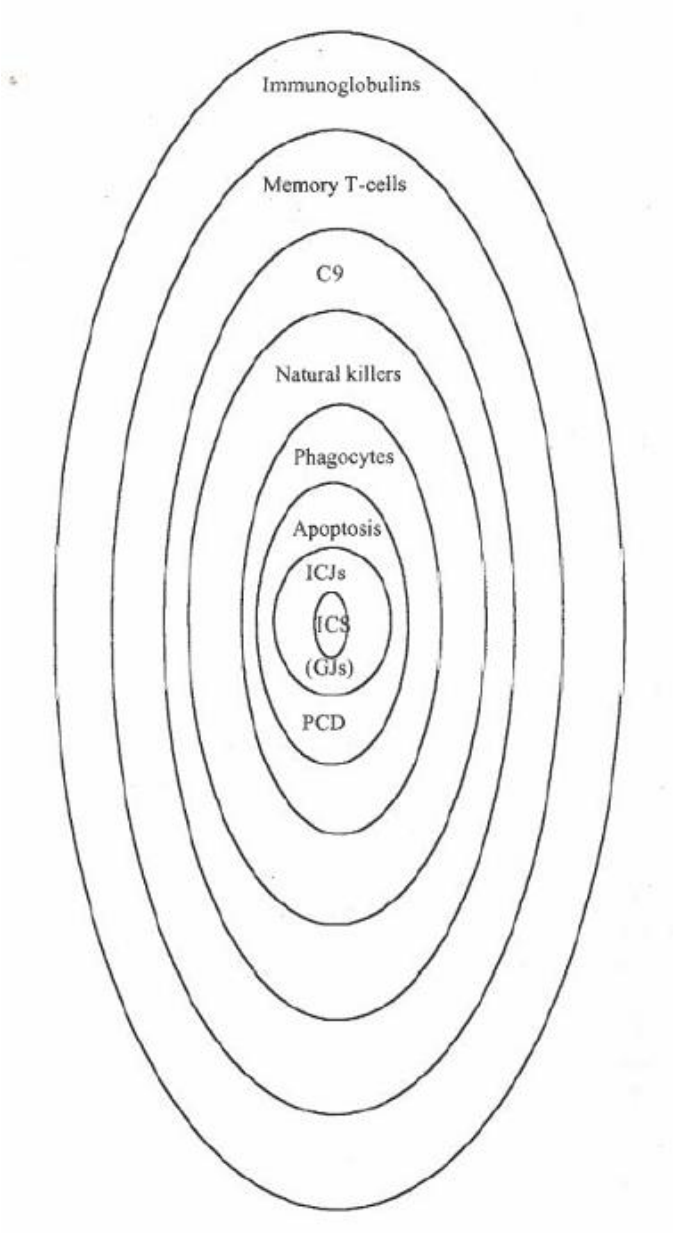
Successful surveillance within the cell leads, where appropriate, to apoptosis and elective suicide. This mechanism deals with most sick cells. When cells die by necrosis, controlled shutdown has failed to protect the ZDC. Now, membranes rupture, their contents are spilled and this promotes inflammation. Inflammation provokes aggressive T-cell responses. When cells rupture, they release a characteristic set of cytokines, particularly eicosanoids. These are the messengers that notify adjacent somatic and inflammatory cells that an uncontrolled catastrophe has occurred. Tc cells are primed to encourage cells to enter apoptosis if they carry markers resembling cells from areas where catastrophic death was previously encountered. Th1 cells remember the inflammatory context in which they first met their epitope. When they reencounter similar peptides they can then turn up the inflammatory "heat". They do not, themselves, kill: this is left to "angrified" phagocytes that become more particular about what they accept as HS identity. In contrast, peptide debris processed after the phagocytosis of apoptotic cells promotes T-cell suppression. For instance, when a cell dies following a virus infection its debris is processed by adjacent cells and phagocytes. If cell death has occurred following successful internal surveillance (apoptosis), tolerance will be promoted to any presented peptide debris, including viral peptide. When unsuccessful (eg, lytic or necrotic death), inflammation will promote T-cell aggression to presented peptides, including self peptides. However, since apoptosis is such a common process, most self peptides have previously promoted suppression and so shrunk the populations of precursor T-cells capable of being recruited into aggression against self. Furthermore, the threshold at which uncommitted T-cells are triggered into aggression falls as they age. This helps to focus aggression onto strange rather than common epitopes.

HS cells in an inflammatory area are relatively immune from self attack because they still demonstrate HS identity. I contend that this is the real horror autotoxicus. Phagocytes from closely related species share a similar specificity. Non-pathogenic organisms are easily identified as non-self. Unless complement is present, bacteria and viruses must rupture a cell and/or disrupt its ICJs to invoke an inflammatory reaction and trigger an anamnestic immune response. Many dedicated pathogens appear to have evolved mechanisms to heighten inflammation in order to create themselves the niche they need to survive (eg, TB).

Inflammatory cells need to be restrained from entering healthy tissues until things go wrong since their intrusion disrupts tissue function. The endothelial cell linings of blood vessels tend to lock out phagocytes until they are invited in. This is done most rigorously in the central nervous system - the blood brain barrier. This barrier is necessary as nervous function relies on the electrical (GJ) disconnection of neurons at their terminal differentiation. The resulting (functional) asynchronisation then makes them more susceptible to macrophage attack (note how traumatic paraplegia is ameliorated with steroids). The need for segregation is likely to be an important factor in the origin of the vascular system and of inflammatory regulation.

Morphostatic evolution

This is the way I suspect that the metazoan system evolved. Note that each new step is an embellishment of the former and all of them remain functional in mammal morphostasis. Each step is a new shell that is superimposed over and complementary to the former shell.



(Figure 1) The heart of the system is the intracellular surveillance of the cell's health. Every cell monitors its internal state looking for dysfunction. Apoptosis is triggered by ill health or inappropriate activity.

(A) Cells develop a sophisticated system of internal surveillance to detect damage, infection and

dysfunction and they do so long before evolving into multicellular forms.

(B) ICJs evolve early in the history of multicellulates and they enhance cell survival. Elective cell suicide (apoptosis) is soon established to protect the colony (it is also seen in plants *(5,6)*). Tissue form remains stable provided cells maintain intimate contact through intercellular junctions. Joined cells establish various degrees of electrical and metabolic synchronisation and this promotes co-operation and survival. Synchronisation and survival are enhanced when the cytoplasms are in direct continuity through gap junctions and more pronounced in synctia. Sick cells sense their own disorder and actively abandon HS identity. They shut down the channels that join their cytoplasms with those of adjacent cells then detach their membranes from them. This process often progresses into apoptosis. This is tidy, elected cell death. Self cells monitor each others' identity. Neighbouring cells and phagocytes ingest apoptotic cells before they burst. Necrosis, or lysis, is untidy cell death: such dying cells burst, spill their contents and so release inflammatory cytokines.

(C) The interaction of CAMs, ICJs and the extracellular matrix gives cells a sense of "belonging". The specificity of the molecular mechanisms that lead to cell adhesion, coupling and connective tissue scaffolding, in effect, give cells a healthy self (HS) identity. Similarly, when HS identity is lost, the connective tissue scaffold is dismantled and the cell "undocks" from its neighbours. This HS identity is responsible for the selective reaggregation that occurs after embryonic cells are disrupted *(8,9)*. Electrical/metabolic synchronisation, established through ICJs, enhances HS identity. ICJ formation is the immediate sequel to cell surface ligand/ligand or ligand/receptor interaction: these molecules are known as Cell Adhesion Molecules, CAMs *(8,9)*. Once paired up, membrane holes in apposing cells form GJs (similar channels are important in plants *(5,6,7)*). IgSF CAMs (eg, N-CAM) develop later to act as a focus on which to build highly permeable GJ plaques. This "multiplier" mechanism will later be adapted to spatter bigger, leaky holes into cells or organisms that do not display features of self (the alternative complement cascade). A complement like cascade mechanism similar to the Bb/C3b et seq cascade evolves as the general agent that recognises cell membranes. In the presence of self markers it leads to GJs and in their absence, to attack.

(D) The progressive expansion of different somatic CAMs lead to subordinate, self within self identities and thus tissue specialisation. These define new developmental compartments where the borders are demarcated by a sheet of cells having GJs of low permeability. The cells within the compartment express IgSF CAMs and are joined by highly permeable GJ plaques. Note that cell sorting is dependent on CAM expression, particularly cadherins *(8,9)*. Homoeotic gene expression has also been noted to change at these compartment boundaries *(20)*.

(E) Animal cells split into dedicated phagocytes and soma. The soma abandons most of its capacity for wandering and aggression. The scavengers abandon most of their capacity for extensive connective tissue scaffolding.

Soma Ligand(s) - for recognition by resident scaffolders

Phagocyte Ligand(s) - for recognition by itinerant scavengers.

Dedicated phagocytes evolve. They refine both their co-operative ICJ communication with self cells and the attack system that inserts leaky holes into non-self cells: the latter will eventually lead to the complement system. Phagocytes are derived from a cell lineage that lies outside the three main germ layers so they may, when they infiltrate somatic tissues, be demonstrating a property akin to the sorting tendency of disaggregated cells: they are able to clamber over all other cell types and envelope them. Phagocytes establish one aspect of selfness by making ICJs with underlying cells. This leads to a degree of electrical/metabolic synchronisation. The specificity of this ICJ connection is at least species wide and recognises selfness that is probably shared by related species. First, the phagocyte uropod establishes ICJ

connections with an underlying cell: then it reaches out lamellipodial fingers to test whether adjacent cells/organisms are synchronised with the uropod attached cell. The trigger for an attack may be the capacitatively induced currents that are generated as membranes come into apposition. The phagocyte uses a variety of additional strategies like, eg, recognising apoptotic cells and, perhaps, surface markers that are indubitably bacterial in origin. Note these points: (1) C9 has a thrombospondin motif that is used, in other circumstances, to recognise apoptotic cells; (2) basement membranes maintain physical barriers between tissues and help to minimise the area of cell membrane contact between different compartments.

(F) A "vascular" system evolves. This is able to lock out most phagocytes till they are required and an inflammatory cascade can now be established. The alternative complement cascade is "humoralised" so that circulating C3 can mark clearly foreign organisms and make them more readily identifiable when they are met by a phagocyte. (It is possible that the perforin-C9 family originated from Tnk cells in order to promote rapid junctional communication between Tnk cells and cells marked with self Mhc Class I ligands. This would act as mechanism for protecting them from attack.)

(G) The specificity and diversity of interactions between N-CAM ligands is achieved by a process of alternative RNA splicing *(8)*. N-CAM like genes can now be adapted to produce multiple different ligands within a herd rather than within a ZDC. These are the ancestors of the Mhc class I genes and will act as cell surface "flags" and are used to advertise a more personalised HS status. They are, probably, only used in crisis (eg, when displaying HSPs - heat shock proteins). At some stage, perhaps even as late as the advent of Tc cells, the identity genes are joined by another duplicated and transposed gene to produce the definitive Class I like Mhc gene *(21)*. This additional gene encodes a pincer mechanism like the HSC70 heat shock proteins (these look after "sick" proteins).

A new cell is needed to recognise these Mhc like identity ligands (the ancestor of Tnk cells). This evolves from phagocytes. It attacks organism membranes in general (Nb that the complement Bb/C3b complex has the same function) but observes a horror autotoxicus to any cell/organism that displays self specific ligands *(22)*. These Tnk like scavengers need a mechanism to produce and/or select self specific receptors unique to each ZDC. This must be done, after meiosis, over a number of mitotic generations - the "generation of specificity". To achieve this diversity in ligand recognition, a mechanism was required to produce many different receptors from which an appropriately specific receptor could be selected - "the generator of specificity". It is from this that the antibody genes have subsequently evolved. Horror autotoxicosis needs redefinition: only HS cells are protected by it. Selection in Tnk cells may be by alternative RNA splicing.

Cell Types And Actions

Cell type	Receptors leading to deletion of cell	Receptors acting as triggers	Untriggered state	Triggered state
Phagocyte		Self CAM?	Aggressive	Passive
NK cell	All other specificities ***GENERATION of SPECIFICITY***	Self MHC plus or minus common self (stress) peptides	Aggressive	Passive
Tc cell	Self MHC plus or minus common self (stress) peptides	All other specificities ***GENERATION of DIVERSITY***	Passive	Aggressive

(H) Note that the Class III Mhc region contains a variety of genes encoding molecules that are involved in HS/OTHS discrimination or its modulation. These include HSP70, TNF, complement components (C2, Bf and C4) , the 21-hydroxylases *(23)* and cytotaxin: the TAP genes are in the Class I region.

(J) Both the complexity and the repertoire of this mechanism for generating and selecting specific receptors is able to evolve gradually. Once the repertoire is large enough, its function can be inverted, so leading to a mechanism able to recognise and attack all other specificities (Tc function). Thus Ts and Tc like cells can now evolve to recognise and, as appropriate, tolerate or encourage apoptosis in cells whose Class I ligands had been altered by the intended attachment of peptides to the pincer mechanism. (Cells that carry strange epitopes - typical of other cells that have previously been associated with necrosis - can be encouraged to procede rapidly into apoptosis.)

(K) TH1 cells evolve as an extension of Tc cell function. The Class II Mhc mechanism evolves from the Class I mechanism: now, short, representative peptides from cellular debris are processed by phagocytes following apoptosis or inflammatory reactions. These are then externalised as a Class II/peptide debris combination ready for the attention of uncommitted T-cells. The "generator of diversity" is now enrolled into creating a system to memorise the inflammatory/non-inflammatory context in which these processed epitopes were first encountered. Cell death without controlled shutdown (ie, without apoptosis) is pro-inflammatory and TH1 cells primed in this situation will, when they re-encounter the processed epitope, attract large numbers of phagocytes to the site and "angrify" them. This gives inflammation a memory. The "angrified" phagocytes still have to sort HS from OTHS but their threshold for regarding a cell as OTHS is lowered. So, neither Tc nor TH1 cells are involved in assessing selfness. They are, instead, primed by other cells, particularly phagocytes, to remember the controlled shutdown/catastrophic death context in which their epitopes were presented to them when they became committed (ie, apoptotic/lytic death discrimination) (24).

(L) The system of tolerance has to evolve hand in hand with aggression. Even though apoptotic cells fragment, each particle is retained in an intact membrane and all are tidily phagocytosed by adjacent cells or phagocytes. The peptides processed in consequence need not - and should not - activate Tc or TH1 cells: rather, tolerance is desirable. However, cells that rupture and spill their contents have not been identified and cleared by the surveillance/apoptosis mechanism. They pose a threat: by releasing eicosanoids and other cytokines they provoke an inflammation and this then leads on to the activation of Tc and TH1 cells.

So, uncommitted T-cells are sensitive to the inflammatory cytokines or non-inflammatory environment they sense when they meet their respective epitope. They become committed accordingly. Self antigens are copious and are regularly encountered in the course of widespread apoptosis. The majority of precursor T-cells with paratopes recognising processed apoptotic debris (the majority of which is self peptide) will be either "mopped up" into a commitment to suppression (tolerance) or clonally deleted. Such T-cells will either be decommissioned or primed to inhibit inflammation on epitope re-encounter. However, uncommitted T-cells with paratopes specific for self Ags continue to be released from the bone marrow and they may be primed rather than clonally deleted in the thymus (where enhanced apoptosis removes most lymphocytes capable of recognising stressed self). At least a proportion of these may become committed to aggression when the inflammatory process is prolonged and foreign epitopes, that accelerate its resolution, are sparse. This system is probably enhanced by the simple expedient of encouraging the threshold - at which aggression can be triggered - to fall as precuror T-cells age. This focuses aggression onto strange epitopes.

The function of precursor T-cells requires them to migrate to and pass through inflammatory nodes. There is a high risk of bystander necrosis in these areas. A protected environment (the thymus) is needed to encourage apoptosis - and so tolerance - of these T-cells in advance of this migration.

(M) The antibody system can now be launched as "icing on the cake". TH1 cells can be adapted to TH2 function and these in turn used to co-operate with B-cells. The B-cells evolve to secrete large quantities of circulating antibody. Antibodies help by opsonising organisms. The alternative complement cascade is now adapted to be triggered by C1,2&4. These have evolved from the ancestral components that are used by N-CAM to spawn GJ plaques. The antibody system is optimised to work within the vascular system. It can interfere with any intended function of the Ag and tag it for enhanced phagocyte attention and attack. This system has proven to be an invaluable pre-emptive defence. (I have presumed that antibodies developed late because it makes current sense. However, there may have been a function that encouraged the early or simultaneous emergence of B-cells to produce IgM like free antibodies.)

Clinical Consequences

There is insufficient space here for a detailed elaboration so here is a whistle stop tour:

Anergy

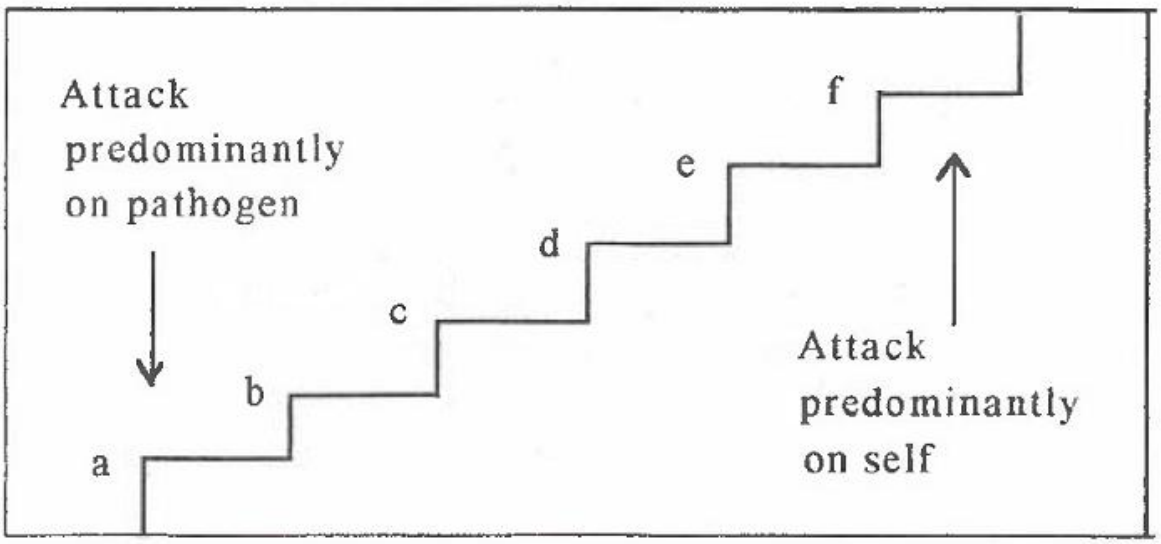
This term has acquired several meanings. Here I am referring to the loss of delayed type hypersensitivity responsiveness that occurs in diseases like TB and cancer. Because the T-helper system is capable of training its aggressive attention on self antigens when clearly strange antigen is sparse (eg, adjuvant arthritis), the immune system must have a failsafe cut-out mechanism. This shuts off phagocyte aggression when tissue destruction becomes too fierce. The effect is intended to be focal though there is often a systemic spillover. It results in foci where surveillance by phagocytes is impaired.

Pathogens

Non-pathogens *(!non-pathogenic organisms!)* are easily identified and eliminated unless there is focal impairment of surveillance (anergy). Pathogens need to devise means of breaching the morphostatic defence. They do so by mimicking, blocking and fooling identity mechanisms *(25)*. Tuberculosis, in particular, deliberately invokes intense inflammation, causing extensive auto-rejection. It then flourishes in a resulting focus of phagocyte impotence.

Auto-Rejection

The result of all this is that any disease that evokes cell necrosis and an inflammatory response develops an element of T-cell augmented auto-rejection. It inevitably consists of a mixture that varies from an attack directed almost exclusively at the pathogen (usually leading to mild inflammation) to an attack directed almost entirely at self (often highly inflammatory): the latter occurs when organisms or cells provoke prolonged inflammation but do not provide or present clearly foreign looking (unusual) epitopes. Every disease that leads to cell damage will induce auto-rejection, even if this goes no further than apoptosis. Because heat shock proteins are responsible for chaperoning disrupted proteins through the cell, they are frequently presented as epitopes in UHS presentations. Auto-rejection rumbles along at a low level all the time. When inflammation is prolonged and no clearly foreign epitopes are present to bring it to a conclusion, precursor T-cells - specific for self Ags - may be progressively recruited into aggressive action. These intensify local inflammation and so enhance tissue rejection. This appears to be what happens in adjuvant arthritis.



(Figure 2) The stepped progression of attack on self. (a) saprophyte; (b) simple epithelial commensal; (c) staphylococci and streptococci; (d) tuberculosis and syphilis; (e & f) multiple sclerosis and sero-negative arthritis.

Cancer

GJ communication between normal and cancerous cells is disrupted (26). There are two broad groups. The first are cancer cells that only communicate with their own kind and make no communication with adjacent normal cells. These are relatively less aggressive and invade locally rather than metastasize distantly. The other group contain cells that also cease to communicate with each other. They are immortal cell lines that have escaped from the usual Hayflick restriction of (about) 50 doublings. (Note that as cell lines age they become progressively poorer communicators through GJs (3) and that they eventually elect to cease to duplicate.) These cancers metastasize haematogenously to distant sites. Phorbol esters, which are cancer promoters, stabilise cells that would otherwise elect for apoptosis. The depression of focal surveillance that occurs in the wake of lymphocyte amplified auto-rejection is at least partially responsible for allowing malignant cells to escape detection and elimination. The final event that leads to immortalisation of the cancer cell line is probably the loss of the ability to effect apoptosis (through the p53 mechanism) when internal surveillance indicates it is appropriate.

Conclusion

The general principles of morphostasis are discussed. I have made a committed assumption that GJs are the most important ICJs in maintaining HS identity. Other ICJs may contribute a larger part than I have credited here. This idea has been constructed using a cycle of speculative hypothesis followed by falsification leading to new hypothesis. By experience, many of its more precise conclusions will prove to be not quite as conceived but they will prove to be closer than the current paradigm permits. If well founded, the hypothesis should prove to be a useful framework for a more focused investigation of the biochemical processes of morphostasis.

Acknowledgments

I wish to dedicate this article to Olwen, David, Rachel and James who have tolerated and supported me through an obsession. Thanks to the Wessex Medical Library who have made this synthesis possible and supplied everything that I have needed.

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(This is not the original article!! It is very similar to the original but I have replaced lots of `which's with `that's and incorporated the corrections that were later printed as errata. I have also brought attention to the point that not all pathogens are living organisms))

Nb, I have used the term "soma" but really I was searching for a term like soma or parenchyma that identifies tissues built on a connective tissue scaffold in contrast to the mobile elements found in blood and lymph.