Setting the scene

Your paper struck a chord for me because of my interest in the philosophy of immunology. I have published various articles around this. I have a website dedicated to it. I note that Cunliffe and "morphostasis" are not mentioned in your manuscript. This suggests, to me, one or more of these possibilities. You:

1) are unaware of the morphostasis model and have not read my various papers
2) do not consider the ideas important enough or mainstream enough to include them for open discussion
3) have not visited my website at https://www.morphostasis.org.uk
4) consider that I have parasitised Polly Matzinger's ideas and reformulated them as my own.

And,

5) also, there seems to be a concerted trend, in immunology literature, to avoid mention of my contributions

Should point 4) be the reason, then this conclusion is wrong.

- The 1985 version of Morphostasis and Immunity emphasised the primacy of the innate immune system
- It also introduced the concept that the initiation of aggressive adaptive immune responses is by damage
- You could also see that these points were raised in response to the various referee's rejections
    - 19920324_crit
    - 19930309_critic1
- and that the following entry establishes the conceptual precedent for the induction of adaptive immune system tolerance by apoptosis
    - 19930718_lymphocyte_commitment
- And this file highlights the frustrations I have experienced in trying to convince others of the concept's potential importance.
- The Unpublished section includes
    - Clinical Morphostasis. This discusses the identity confusion between self-cells and microbes that, I suspect, contributes to the pathogenesis of the sero-negative arthritides. It also includes
    - The neurology of Behçet's syndrome (this is "where it all started").
    - Flushing out the phlogiston? For me, this is my most insightful piece.
    - The danger theory: 21 years later – this emphasises the inflammo-centric nature of immunity.

It is possible that my letters and submissions (with their rejections) somehow percolated through to the wider immunology community before 1994 and influenced other people's ideas. Should you delve into the history of the concept (visible at my website where the various versions and communications are reproduced), you would find that the key points that Polly introduced were included in submissions sent to various journals and immunologists well before Polly's seminal article in the Spring of 1994. These were met with serial rejections by reviewers and none of the people I corresponded with seemed to be impressed with the potential importance of the concepts. In her acknowledgments at the end of her 1984 article, Polly makes it clear that "responding to danger signals" was not her own idea; Ephraim Fuchs had to work hard to convince her of this perspective's importance.

As far as I know, Polly has never recommended people to look at my work. This might be explained by point 2); it is not 1) and shouldn't be 4). She certainly knows me; I drove her from Harrogate to the airport in December 1998 when we had a long discussion about our mutual interest. It was clear, when I introduced myself to her there, that she knew of my work and understood its potential importance.

Crying over spilt milk is churlish; complaining about this just for personal (animal) recognition would be ugly rhetoric. If, for some reason, the immunology community wishes to ignore mention of my concepts, then I cannot complain (even though I can try to bring attention to it). However, if anyone is deliberately suppressing reference to my contributions just to protect their own claim to key ideas, then this would be a "crime" against the group intellect that emerges from scientific enquiry. There are ideas and concepts in here that, I believe, the world of immunology should ponder. My "ownership" of them is irrelevant except inasmuch as it could arm me with greater "street cred" to help air these ideas more widely and, possibly, have them adopted/adapted into the extant consensus (should they deserve this).

So, I reckon that I have established a track record that justifies me in commenting on some of the points that you have raised. That is what I will do now.

My comments on your paper

Immunology is rife with assumptions, presumptions and metaphors. Many of these have accumulated because immunologists *en bloc* became preoccupied with humeral factors, lymphocytes and anamnesis. Metchnikoff's cellular approach is regularly lauded in textbooks before rapidly dashing off to deal with much more important things about

lymphocytes and antibodies. This is a legacy to the way that the investigation of immunity has proceeded. Should it have followed Metchnikoff's lead in the early 20th century, I believe this would have avoided an obfuscating focus on the discipline's overwhelming preoccupation with adaptive immunity.

There are hidden assumptions in the old accumulation of ideas around self/nonself discrimination. A paradigm grows up by generating its own supportive "facts" ; but facts are mostly observations biased by explanatory assumptions.

- "Pathogens" are increasingly defined as living, biotic agents. Once we emphasise that a pathogen is (generically) just an injurious agent, the immune system's response to pathogenic micro-organisms takes on new meanings.
- Early immunologists formulated the concept of S/NS discrimination "by the immune system". But, the theory that emerged is that this discrimination is carried out almost exclusively by the ***adaptive*** immune system. It was assumed that antigenic ***epitopes*** are categorised into self (learned in utero – but what about frog spawn and tadpoles?) and nonself (everything that turns up later). This persisted even when it became clear that the alpha-beta T-Cells recognise short peptide chains of ***chopped up intracellular debris*** in an Mhc groove. We should have paid more attention to the debris origin – it's already processed and chopped up by antigen presenting cells.
- This self/NS theory predicted that self-reactive lymphocytes needed to be culled in the thymus. This is now, at least in part, clearly wrong, if not dominantly wrong. T-reg activity is intimately involved (a recent Nature Reviews Immunology summary of a Science paper expands on this).
- It was firmly assumed that the immune system is dominantly lympho-centric; lymphocytes are in command and control. I am convinced that an inflammation-centred view is almost certain to prove much more useful and accurate. As far as I know, this was not part of Polly Matzinger's formulation.

I contend that self/nonself discrimination is very much alive BUT I don't believe it is managed by lymphocytes. Every healthy cell derived from the zygote uses identity cues to communicate with and respond to its healthy neighbours. One of the ontologically earliest expressions of this is how disrupted embryonic cells reaggregate according to tissue type. They "know" where they belong. Indeed, the molecules that command this identity mechanism are extensively adapted and re-deployed in various molecular immune cell mechanisms.

A good place to start is with "What does self nonself discrimination by the immune system entail". But, before that, what is the immune system and what is its overriding "purpose/preoccupation". Because infective diseases were so prominent in our perceptions, and because of their moderation by immunity, "fighting" micro-organism infections was perceived to be the primary (if not the whole) purpose of the immune system.

The ideas around humeral factors came to be regarded as the dominant and commanding factors in the "fight" against infection. This left innate immunity out on an "also ran" limb that received brief lip service before getting into the real meat of immunology. However, it was always likely that inflammation both drives and acts as the effector for the adaptive immune system; but the discipline remained blind to the actuality that the adaptive immune system provided both an amplifying and memorising mechanism for prior inflammatory encounters.

The other "blinding" presumption was that the immune system is an exclusively aggressive mechanism whose purpose is the killing and disposing of pathogenic micro-organisms. Now, it is becoming increasing apparent, the immune system is involved in a panoply of physiological mechanisms way beyond this simple (and naïve) view. It is now also clear that the immune system has an active, anamnestic tolerating function (see the article quoted above).

So what could be considered self? We can start that off by brainstorming self. Self implies identity in some form or another. This is not intended to be a complete list but it does help to outline the facets that a morphostatic system has to deal appropriately with.

- Zygote derived cells (ZDCs)
    - Healthy self ZDCs, in the right location and behaving appropriately are tolerated and nurtured
    - Self cells that need disposal
        - Catastrophic death with cytoplasmic spillage (highly inflammatory)
        - Controlled self ZDC cell shutdown with "silent" disposal ("I know I'm dysfunctioning" cells)
        - Ectopic cells (eg, red cells that escape into tissues – bruising; also metastatic cells)
        - Redundant cells (eg finger webs and the uterine lining in a cyclical fashion)
        - Anarchic self ZDCs (potentially malignant)
        - Cellular scaffolding may need dismantling and reconstruction
        - All of these need replenishment and proceed to a resolution of damage by regeneration
        - Continuous disposal of circulating blood cells, once past their "sell-by" date (eg, blood groups and splenic filtration".
- "Membership" identities
    - Species-cell membership – a likely broad identity

- Tissue-cell membership – tissue site identity leading to local co-operation
- Kingdom-cell membership (viruses and bacteria are “foreigners”)
- Acceptable and useful visitors (colonisers, eg, slime moulds ***farm*** their preferred bacteria).
- Tolerable visitors (viruses and other micro-organisms that do little harm, they may even provide useful genes and metabolites. We now believe that mitochondria are obligate bacterial residents, to the point that they have become an essential and integral constituent of the colony of zygote derived, healthy cells.

Then we have discrimination.

An essential part of the self nonself paradigm is that various opposites are distinguishable. The old view naïvely saw this discrimination as a mechanism that sorted all encountered ***epitopes*** (antigens – mostly proteinaceous matter that span around 20-30 amino acids) into those found associated with self cells - largely learnt “in utero” - and those not encountered “in utero”. Because the immune system was seen as a bug finding and fighting force, all anamnestic immune activity (courtesy of T- and B-cell function) was regarded as intrinsically aggressive. So elimination of self reacting T- and B-cells in utero was the natural presumption to account for self-tolerance. Should this presumption prove to have been wrong, it is probably still going to suffer a lingering demise within a cohort of dedicated proselytists. However, we only have to find ***some*** evidence of active anamnestic immune (foetal thymic) tolerance to expose this as a flawed presumption (that is, I contend, now confirmed).

I have noticed that prominent immunologists have sometimes used crossed pairs for discrimination (like self/pathogen discrimination) and this is both illogical and obfuscating. We can imagine a panoply of possible discriminations and then analyse the likelihood of their individual or corporate involvement in the discrimination process.

The body may discriminate on the basis of one or many of the following opposites.

- [self epitope] vs [non- self epitope]
- [self organism] vs [non-self organism]
- [healthy self epitope] vs [other than healthy self epitope]
- [healthy self cell] vs [other than healthy self cell]
- [zygote derived cell] vs [non-zygote derived cell]
- [eucaryotic-cell] vs [non-eucaryotic-cell] (bacteria a major constituent of the latter)
- [diseased] vs [non diseased]
- [pathogen] vs [non-pathogen] (we need to define pathogen accurately)
- [foreign organism] vs [non foreign organism]
- [damage] vs [non-damage]
- [danger] vs [non-danger]
- [dangerous] vs [non-dangerous]
- [tidy tissues] vs [untidy tissues]
- [mess] vs [non-mess]
- [order] vs [disorder]
- [homunculus] vs [non-homunculus]
- [electrically synchronised] vs [electrically unsynchronised]
- [psychological self] vs [psychological non-self]
- [self-species cells] vs [other-species cells]
- [one tissue’s cells] vs [another tissue’s cells] (eg, epithelial vs mesothelial or liver vs kidney)

Even:

- [self] vs [non-self] (but we know this is bedevilled by multiple possible definitions of "self")

And there are probably many other possibilities.

And, so we could go on. There is a good chance that many of these will prove to be involved to some degree or another. And, that makes the self epitope vs nonself epitope idea begin to look embarrassingly quaint and naïve; this idea was, in retrospect, absurdly Heath Robinson.

The old perception that the immune system discriminates self from non-self grew to an ” idée fixe” that has, arguably, crippled conceptual progress in immunology. Even its protagonists did not spell out precisely what they were advocating; this was categorising all potential ***epitopes*** (antigens) into those found in association with self (zygote derived components) contrasted this those associated with non-self (the rest). With all the potential crossover of possession, this always looked shaky.

An ” idée fixe” needs an hysterical exorcism to overcome the crippling hegemony imposed by a fanatical adherence to the old ideas. Only then can we subsequently come back and consider rehabilitating the best parts of the old ideas (but now they will be viewed from an alternative perspective). Self/non-self discrimination by ***epitopes***, I propose, was ridiculously naïve and came about because it was the simplest (simplex) explanation. Its naïvety was only challenged from the late 1980s onwards.

The very formulation and the idea of discrimination by the adaptive immune system, of self from non self and of pathogen attack, was built on but a small selection of the cells associated with the immune (or morphostatic) system (alpha/beta T-cells and B-cells). This constricting viewpoint has been obfuscating in the extreme.

The following elements are all involved in the immune (morphostatic) system.

- Cell death (elective, induced and catastrophic forms)
- Complement and its evolution
- Debris management (both intra- and extra-cellular)
- The capacity to regenerate and restitution (a proportion of self cells can be safely sacrificed)
- Cell check point controls
- RNA interference
- Heat shock proteins and ubiquitins (the cell’s garbage minders)
- Membrane perturbations and the prostaglandin system
- A host of inflammation, phagocyte and T-cell/Bcell-related chemokines
- Several fulcral genes (P53 and NF-jB immediately spring to mind)
- Apoptosis
- Autophagy
- Protozoa make a mate or meal discrimination
- Phagocytes and inflammation (plus other cells like mast cells)
- Natural killer cells
- Various innate immune cells
- T-cells/B-cells/antibodies (the adaptive immune system)
- Gamma-delta T -cells

Self cell death captures the vast majority of the adaptive immune system’s attention; and that exposes its other preoccupation – the regeneration of lost tissue and the restoration of form. It is dominantly concerned with classifying prior encounters into those associated with controlled cell shutdown (tolerogenic) and catastrophic cell death (for example necrosis and cell content spillage]. This is what the adaptive immune system discriminates. There is no failsafe protection against self-directed immune aggression other than a mass action effect where prior effete cell are shut down in a controlled fashion. This tends to mop up representative epitopes into tolerance. Strange epitopes, seen for the first time in association with catastrophic cell death, easily lead to aggressive responses and, in consequence, this favours epitopes found associated with pathogenic microorganisms.

The old concept of a horror autotoxicus to self-antigens is bankrupt. To overcome the immune system’s reluctance to attack self, you only have to pulverise brain (or some other tissue) with a strong adjuvant and then inject this repeatedly. But, horror autotoxicus is still probably “alive”; it is the strong reluctance to attack healthy ZDCs that are behaving appropriately in their correct location

After any significant change of concept, the chasing cohort tends to reify their conceptual heroes’ speculations (for that was what they were before general adoption). These then become the new dogma that becomes heresy to challenge. Both Metchnikoff and Burnet had incredible prescience that reification subsequently leads us to ignore.

I could go on and on. The simplistic lymphocyte based idea of self-epitope nonself-epitope discrimination has so dominated and confounded our perceptions that it is hard to escape from them.

More can be found at my website. It would be rewarding to find that someone considers this challenge to the conventional view is worth exploring.