



## A mechanistic theory explaining hyperferritinaemia in haemophagocytic lymphohistiocytosis

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### ABSTRACT

Intracellular ferritin is known to store iron, an essential element in an array of physiological processes. But what purpose does serum ferritin serve, what controls ultra-high hyperferritinaemia (ferritin levels above 4000 ng/ml), and finally why is it raised in inflammatory diseases, the most impressive being haemophagocytic lymphohistiocytosis? This paper proposes a hypothesis and model to explain the above questions.

Serum ferritin has some unfamiliar physiological properties. It dampens severe inflammation by inhibiting lymphocyte activity, hinders bacterial growth by acting as an iron chelator and slows malignant growth by having an antiangiogenic effect. Therefore, serum ferritin is effective at modulating many conditions and could be a desired physiological process in malignancy or infection.

The proposed theory is that phagocytic cells fuse with pathological native cells in much the same way as macrophages do when forming multinucleated giant cells. The pathological cells can be “infected” by intracellular pathogens or the malignant phenotype. These fusion cells result in a massive upregulation of exclusive features of macrophage activity such as phagocytosis, iron metabolism and ferritin release. Dysfunctional mitochondria are critical to this process, Pathological cells that contain dysfunctional mitochondria “infect” phagocytic mitochondrial following cellular fusion, resulting in ferritin release.

The key evidence supporting this idea: macrophages are the source of ferritin secretion; they have intimate contact with known triggers of HLH, allowing for fusion hybrids, and they commonly fuse with cells. It is also argued that exclusively intracellular pathologies trigger HLH, which is a requirement for this model. HLH has features of a mitochondrialopathy and finally it is debated that all the defective genes known to trigger familial-HLH can increase the likelihood of macrophage fusion. If this hypothesis is correct, the implications might discover novel diagnostic tools to detect HLH and point to avenues of targeted therapy.

This is a bold theory with interesting perspectives on cell biology and clinical medicine. The paper discusses the evidence and challenges of this proposed mechanism in describing hyperferritinaemia and its relation to HLH.

### Introduction

Two well understood causes of hyperferritinaemia are iron overload and hepatic injury. Excessive iron accumulation spills ferritin into the circulation and liver diseases cause stored ferritin release via damage to hepatocytes, in much the same way as alanine aminotransferase is raised during hepatic injury. These conditions have simple mechanisms, rarely cause ultra-high hyperferritinaemia (UHH) defined as a ferritin level above 4000 ng/ml and will not be discussed in this article.

The question of why ferritin is secreted in such large quantities in the presence of advanced cancer, infection and allegedly autoimmune illnesses point to a different pathophysiological process to that seen in hepatic injury and haemochromatosis [1–5]. Why hyperferritinaemia is so common in these conditions is an intriguing question. One of serum ferritin's actions is dampen severe inflammatory response syndrome, in an attempt to ‘calm’ the immune system to prevent the host destroying itself [1]. Severe inflammatory response syndrome can cause multi-organ failure, requiring intensive care and sometimes steroid use, another immunosuppressant. Ferritin, like steroids has an inhibitory effect on lymphocyte division and granulocyte production, both of which are

necessary to maintain an inflammatory response [1].

Ferritin also scavenges free iron, depriving bacteria and cancer of this micronutrient which is essential for their proliferation. There is also *in vitro* evidence that ferritin modulates angiogenesis, affecting the growth of solid tumours and administering serum ferritin has an anti-tumoural and antimicrobial effect [1]. In summary, serum ferritin may reduce the destructive nature of an overly aggressive immune system and inhibit bacterial and tumoural growth. Therefore, UHH may be an adaptation for the above illnesses, but what is the mechanism that describes how hyperferritinaemia develops?

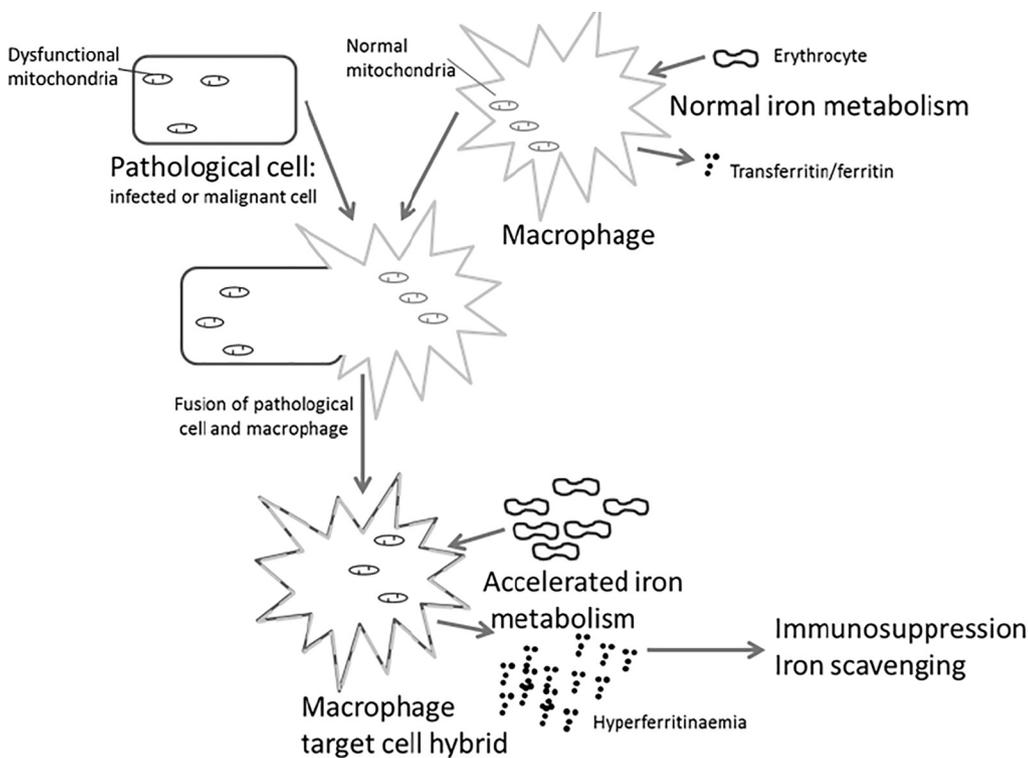
An important disease that is not well understood and triggers UHH is haemophagocytic lymphohistiocytosis (HLH). This disease is characterised by severe inflammation, haemophagocytosis, hyperferritinaemia and has a high mortality if not treated aggressively. It might be that the most hostile cases of UHH are diagnosed as having HLH and therefore share the same pathophysiological mechanisms. There is to the best of our knowledge never been an in-depth description of a proposed pathophysiological mechanism for the observed UHH in HLH, but this will be attempted in this paper.

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**Fig. 1.** The mechanism of hyperferritinaemia and HLH. Macrophage mitochondria have the innate ability to phagocytose erythrocytes, metabolise iron and secrete ferritin. Macrophages also possess the ability, on occasion, to fuse with pathological cells. The pathological cells that trigger HLH have toxic mitochondria, usually caused by intracellular infections or malignancy. Once this fusion ensues, it is proposed that the toxic mitochondria from the target cell ramp up the normal iron metabolism occurring in macrophages. This hybrid cell is haemphagocytotic and chews up erythrocytes and secretes ferritin.

#### *The proposed theory explaining hyperferritinaemia in haemphagocytic lymphohistiocytosis*

Mitochondrial macrophages have a unique ability to recycle iron and pump out ferritin, it is the macrophage that is therefore integral to the pathophysiological process of UHH and HLH. Macrophages and other phagocytes also have the unique ability to fuse with pathological native target cells, forming fusion cells. Following this fusion, any “toxic” mitochondria from the target cell can activate a state of massive iron metabolism and ferritin secretion in the newly formed fusion cell by stimulating macrophage’s mitochondria. These pathological target cells could be infected by pathogens or by malignancy. Both intracellular pathogenically infected cells and cancer cells are known to have toxic mitochondria. In an effort to continue to secrete ferritin, the newly formed fusion cells with abnormal mitochondrial will phagocytose erythrocytes in order to continue this process of ferritin secretion. These hybrid cells could be the cause of HLH and other conditions of UHH. The mechanism is described in Fig. 1.

In this article macrophage activation syndrome (MAS) is considered another form of HLH. They both have similar clinical and pathological features, but MAS is considered to be caused by rheumatological diseases.

Although this theory seems implausible, the supporting evidence is convincing and fits in with observations in the literature [2–5]. This is we believe the first attempt to describe a model of the pathophysiology of HLH and UHH that fits in with the known observations of HLH and related diseases. The implications of this model can have impacts in further research into the diagnosis of HLH and guiding treatments.

The idea evolved from first making the leap in understanding that serum ferritin might be a desired and adaptive response to infection or cancer and then considering a mechanism that would manifest hyperferritinaemia in the setting of these pathologies. Following Professor Seyfried’s work [6] which discusses the origin of metastatic cancer being a malignant cell macrophage fusion product, a similar mechanism could be the trigger UHH and HLH. For the theory to be correct many observations should be documented in the literature and certain observations should not be found, these are discussed in the paper. We

will explain the stages of the mechanism step by step and evaluate the available evidence.

#### **Mechanism of hyperferritinaemia**

##### *Step 1. Macrophages undergo erythrophagocytosis and secrete ferritin*

The established view is that the reticuloendothelial system, which largely consists of macrophages and monocytes (immature macrophages), phagocytose erythrocytes at the end of the red blood cell’s life cycle [7]. The iron from erythrocytes are then secreted as transferrin and ferritin into the circulation. Iron metabolism is not completely understood but what we do know is that it is performed by the macrophage mitochondria [8] the relevance of which is discussed below.

##### *Step 2. Macrophage intimacy with target cells*

Macrophages are attracted to sites of inflammation that are often triggered by bacterial and viral infection and are often the first to encounter these agents, interacting with them intimately. Malignant tissue also triggers inflammation and attract macrophages in much the same way and are labelled tumour-associated macrophages [9]. These first two steps are well-recognised processes in cell biology. The following steps are known in established literature but are not so familiar.

##### *Step 3. Macrophages fuse with target cells and form hybrids*

Macrophages can fuse with other cells; a typical product of this process is the well-recognised multinucleate giant cells seen with certain infections, like tuberculosis [10]. Cell to cell fusion is limited to a few cell types such as phagocytic cells and is an established phenomenon in cell biology [11]. Classically the fusion is between a macrophage and a cell infected with an intracellular microorganism, however, there is plenty of observational evidence demonstrating that macrophages fuse with malignant cells and also form hybrids [12–14].

Incidentally, it is surprising to most readers that the fusion between macrophages and malignant cells may be the origin of metastatic cells.

Here are some observations from Seyfried et al. papers [6,13] supporting the argument that metastatic cancer cells are in fact macrophage fusion cells with target cells:

- Phagocytosis is a typically conserved feature of phagocytic cells but has been observed in many metastatic tumour types. This can be explained by viewing metastatic cells as having a macrophage heritage.
- The migratory path of a metastatic cell is similar to the route a macrophage travels. Metastatic cells travel first to a regional lymph node and then to distant sites, typically a site with high macrophage turnover such as the liver, lung, bone marrow and sites of inflammation.
- There is evidence of macrophage specific antigens in a wide variety of metastatic cancer cells.
- Tumour-associated macrophages make up a large bulk of tumour tissue and are in direct contact with cancer cells. This intimate and common contact allows fusion to occur.
- Human phagocytic cells and murine melanoma cells have been demonstrated to fuse and have been confirmed by gene analysis and histopathology to be hybrids. This phenomenon is also observed in case studies of patients who develop cancers after allogenic bone marrow transplantation, where metastatic cells had graft and host genetic makeup.

A more recent article covers a raft of experimental evidence that confirms the existence of macrophage-neoplastic fusion cells and their importance in metastatic malignancy [14]. The mainstream counter argument for metastatic cells is the epithelial-to-mesenchymal transition theory, which many pathologists doubt as it does not explain all of the metastatic cell's characteristics and it has not been seen in the laboratory [15]. The macrophage fusion hypothesis explains metastatic origin well and adds credibility to the pathophysiology described in the development of HLH, as HLH can be triggered by malignancy.

Therefore, it is understood that macrophages can and do form hybrid cells with pathological targets. These targets can be malignant cells or cells infected by microorganisms.

#### *Step 4. The toxic mitochondria in target cells activate macrophage mitochondrial iron metabolism following fusion with macrophages*

Evidence that target cells possess toxic mitochondria and that it is this that triggers macrophage mitochondrial iron metabolism, erythrocyte phagocytosis and resultant serum ferritin secretion is difficult to find. This is most likely because research has not focused on studying this phenomenon.

What supports the idea that toxic mitochondria activate macrophage mitochondria is that the known triggers of HLH and other causes of UHH are all known to be intracellular diseases with toxic mitochondria. The next set of paragraphs will discuss the evidence for this.

#### *Toxic mitochondria are a conserved feature of cancer*

Cancer is an established trigger of HLH and therefore for this theory to be acceptable there must be evidence that cancer cells have mitochondrial dysfunction. This is a controversial idea that is a re-emerging concept in cancer biology. Malignancy is a metabolically driven disease, dependent on glycolytic activity in part due to a declining mitochondrial function with reduced oxidative phosphorylation [13,16]. Although this idea is not conventional it is a growing notion in cancer biology and is now an accepted hallmark of cancer, “reprogramming of cellular energy metabolism” [17] and gives credibility to the theory discussed.

#### *HLH viral triggers are toxic to the mitochondria*

Interestingly, the commonest viruses that cause HLH are known to damage the respiratory pathway of mitochondria. The commonest viruses that trigger HLH are viruses of the herpes family, including Epstein-Barr virus and cytomegalovirus, hepatitis viruses and human immunosuppression virus (HIV) [18]. All of these are known to disrupt oxidative phosphorylation in the mitochondria [21]. The herpes family viruses can cause an electron leak from the electron transport chain which results in reactive oxygen species formation and further mitochondrial damage. This is a sure sign of mitochondrial injury and results in a reduction in oxidative phosphorylation. HIV and the hepatitis B virus disrupt mitochondrial membrane potentials, which also results in a reduction in adenosine triphosphate (ATP) production. These viruses have toxic effects on the mitochondria, best described in the cytomegalovirus model [22]. Finally, a case series of UHH [23] demonstrates a preponderance of dengue viral infection and this virus is also known to cause mitochondrial harm and hinder bioenergetics [24].

One might ask why there might be so many viruses toxic to the mitochondria. By damaging the mitochondria, oxidative phosphorylation is reduced, as this is the exclusive role of these organelles. ATP production is then switched to the only other form of energy production – anaerobic respiration, resulting in biomass production, and an anabolic state, necessary for viral assimilation and cell division, both resulting in further replication of the virus.

It may not at first be apparent that anaerobic respiration results in an anabolic state until you review the consequences of carbon along the two exclusively available energy production pathways which are anaerobic respiration and oxidative phosphorylation. In the latter, ATP production is most efficient when the mitochondria oxidises carbon fully to carbon dioxide, which is then ventilated out of the body. Therefore, in oxidative phosphorylation, carbon is lost and cannot be used for biomass production and viral assimilation or cell division. In contrast, in anaerobic respiration or aerobic fermentation (Warburg effect [25]), small amounts of ATP are made and carbon is partially oxidised to pyruvate, acetyl CoA and other intermediary compounds. These intermediary carbon molecules are essential for cellular and viral macromolecular production which is exactly what is required for successful viral replication and cell division.

From this perspective, it makes sense that viruses damage mitochondria, oxidative phosphorylation, and increase glycolysis and anabolism. It is unsurprising that these viruses are also commonly associated with cancer because they promote metabolic pathways that encourage biomass production and cell division, a hallmark of cancer [26]. Incidentally, this is the bases of the metabolic theory of cancer [6,13] and partially explains why malignant cells have mitochondrial damage.

There is an intriguing observation here: viruses that cause HLH are also mitochondrial pathogens, in distinction many other common viral infections are not mitochondrially toxic and not triggers of HLH.

#### *Non-viral pathogenic triggers of HLH are intracellular pathogens with mitochondrial toxicity*

In of itself, it would be fascinating if all the infectious microorganisms that are known to cause HLH were intracellular pathogens, as this would suggest that this intracellular characteristic would be fundamental to the process of HLH, as described in this theory. This is close to what we actually find in observation; all the known organisms that trigger HLH are in fact intracellular when hostile.

Table 1 is a list of the commonest microorganisms known to trigger HLH [18]. Nearly all have an intracellular invasive capacity. Furthermore, it is possible that fungi, the only organisms accepted to be an extracellular HLH trigger, is confounding and not a trigger after all. As pointed out in Table 1, fungal infections are often associated with severe immunosuppression as they often occur in patients with AIDS,

**Table 1**

Bacteria, protozoa and fungi that are known to trigger HLH and their intercellular invasive capabilities. There is a predominance of intracellular pathogens in this list [18].

Organism	Extracellular or intracellular classification
<b>Bacterial</b>	
Mycobacterium	Facultative intracellular pathogen
Campylobacter	Obligate intracellular pathogen
Mycoplasma	(Becomes intracellular when pathogenic) [19]
Chlamydia	Obligate intracellular pathogen
Legionella	Facultative intracellular pathogen
Typhoid	Facultative intracellular pathogen
Rickettsia	Obligate intracellular pathogen
Brucella	Facultative intracellular pathogen
Ehrlichia	Obligate intracellular pathogen
Lyme	(Can evade the immune system by hiding inside cells) [20]
<b>Protozoan</b>	
Leshmania	Obligate intracellular pathogen
Malaria	Intracellular pathogen
Toxoplasmosis	Intracellular pathogen
<b>Fungal</b>	
	(Occurs most commonly in the setting of AIDS, lymphoma, chronic steroid use and transplant recipients) [18]
Fusobacterium	Not intracellular
Candida	Not intracellular
Cryptococcus	Facultative intracellular
Pneumocystis	Obligate intracellular
<b>Viruses</b>	
	All are obligate intracellular

lymphoma, chronic steroid use and in transplant recipients. It is likely that these immunosuppressed patients have other unrecognised intracellular infections that could be the actual cause of their HLH, showing that candida and Fusobacterium are not actual HLH triggers but confounding features. This leaves the theory unchallenged.

To test the robustness of this idea, consider whether usual pathogens cause HLH or not. If you believe, as many do, that HLH is a response to overwhelming immunological activation, often by severe sepsis [27], then you would expect familiar causes of sepsis to trigger HLH. The most common causes of sepsis found in hospital are: *Haemophilus influenzae*, *Streptococcus* genus, *Staphylococcus* genus, *Escherichia coli*, *Klebsiella* genus, *Enterococci* genus, *Clostridium* genus and *Pseudomonas aeruginosa* [28]. These agents often cause sepsis, but none are HLH triggers and none are intracellular pathogens. The proposed model predicts that only intracellular pathogens can trigger HLH and this might account for why we do not see any common extracellular pathogens causing HLH.

#### Toxic mitochondria in HLH

Unsurprisingly, it appears that no investigations into the mitochondrial function in haemophagocytic macrophages in HLH have been done, as this is a novel concept. However, one feature that indicates the involvement of mitochondria in the pathogenesis of HLH is that hypertriglyceridemia is a common phenomenon in HLH [27] and part of its diagnostic criteria. Other than in nephrotic syndrome and chronic renal failure, where dyslipidaemia is thought to be due to nephrotic wasting of lipolytic enzymes which results in a loss of lipid clearance, all other causes of hypertriglyceridemia are secondary to mitochondrialopathies [29]. Mitochondriopathies include: metabolic syndrome [29], Reye's syndrome [30] and lipodystrophy secondary to anti-HIV medication [31].

#### Other supporting features of this model

##### The HLH-2004 diagnostic criteria

Interestingly, the diagnostic criteria for HLH published in 2004, points to the proposed pathophysiological pathways in this article.

Table 2 demonstrates the criteria that needs to be met to make a diagnosis of HLH.

These criteria indicate the following in HLH's pathophysiology:

- **Fever, splenomegaly and hypofibrinogenaemia** criteria are typical in inflammatory conditions.
- **Cytopenia and haemophagocytosis** point to the nature of macrophages phagocytosing erythrocytes and other bone marrow derived cells.
- **Hypertriglyceridemia** is evidence of mitochondrial toxicity [29].
- **Low or absent Natural killer activity** supports the involvement of an intracellular pathogen. Natural killer cells target intracellular pathogens [32].
- **High Soluble CD25 levels** are a feature of mononuclear cell activation [33].

Looking at the criteria, you can deduce that the important features of the pathophysiology are:

- Systemic inflammation.
- Macrophage phagocytosis.
- Mitochondrial toxicity.
- Involvement of intracellular pathology.

All these features are accounted for in the model described above.

*The molecular mutations of familial HLH fail to lyse targets, fuse with their target cell and later fuse with a macrophage*

Familial HLH (F-HLH) is a rare but significant cause of UHH. How does F-HLH fit into this model? F-HLH is caused by defective genes that are all involved in the cytotoxic activity of cytotoxic cells [27]. It is possible that in the intimate contact stages of cytotoxicity while deploying cytotoxic machinery on their target cells, the cytotoxic cell undergoes fusion and forms a hybrid cell. Once these hybrid cells are made they go on to also fuse with macrophages. If the initial target cell contains toxic mitochondria, then it could begin the pathophysiological mechanism described above. Let us now review the defective genes known to occur in F-HLH and evaluate if they are implicated in the intimate act of cytotoxicity [27] as this would support the proposed theory.

40% of F-HLH is caused by a defective perforin protein which is used to create death inducing pores to its cytotoxic cell targets and therefore is indeed deployed at close contact. If during close cell to cell interaction, lysis of the target cell is not achieved, then fusion is indeed a possibility. Munc protein defects are also found in familial cases of HLH and prevent exocytosis of cytotoxic granules on its targets during contact. Again, intimate contact without lysis can result in target-macrophage fusion. Chediak-Higashi syndrome has a predisposition to HLH as a result of a defective lysosomal trafficking regulator gene. Lysosomes contain the cytotoxic granules necessary for cytotoxicity which are discharged while cells are adjacent to each other. Two other gene defects which cause F-HLH are both expressed as proteins involved in cytotoxic cell trafficking, gene STX11 and RAB27a. Fig. 2 shows how the F-HLH defective proteins are involved in the cytotoxic pathway.

It is unlikely to be a coincidence that all the gene mutations known to cause F-HLH are required to destroy their targets in the last stages of intimate contact. Is it possible therefore that cell fusion occurs due to cytotoxic cells failure to lyse their target during close contact? This would account for all the mutations that cause F-HLH to be involved in cytotoxic machinery.

The second fusion that is required in this process is that of the target/cytotoxic cell hybrid with a macrophage. This phenomenon has been extensively researched by Braçq et al. [34].

**Table 2**  
Diagnostic criteria for HLH [27].

<p>In the absence of a gene mutation consistent with familial HLH, an HLH, diagnosis needs five out of the eight following diagnostic criteria:</p>	<ol style="list-style-type: none"> <li>1. Fever. Duration &gt; 7 days, peaks <math>\geq 38.5</math> C</li> <li>2. Splenomegaly</li> <li>3. Cytopenias (affecting <math>\geq 2</math> of 3 lineages in the peripheral blood)</li> <li>4. Hypertriglyceridemia and/or hypofibrinogenemia</li> <li>5. Haemophagocytosis in bone marrow, spleen or lymph nodes</li> <li>6. Low or absent NK-cell activity</li> <li>7. Elevated ferritin <math>\geq 500</math> <math>\mu\text{g/L}</math></li> <li>8. Elevated soluble CD25 (i.e., soluble IL-2 receptor)</li> </ol>
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**Discrepancies with this theory**

*Rheumatological triggers of HLH*

The proposed theory cannot account for how autoimmune diseases would trigger HLH unless some fundamental ideas are challenged. Autoimmune diseases are not intracellular conditions, which is fundamental to the theory described but are caused by self-reactive immune responses. Therefore, this model must be rejected, unless rheumatological HLH triggers commonly referred to as MAS is incorrect.

Rheumatological conditions may be associated with HLH but not caused by them. The association may be confounding. The connection may lie with immunosuppressive agents being used to treat autoimmune conditions that result in opportunistic intracellular infections which trigger HLH. Fig. 3 describes the relationship between the commonly considered triggers of HLH and how they would fit into the model under discussion.

A brief literature review of four case series examining MAS reveals that rheumatological diseases are implicated infrequently. In the few cases in which MAS is determined to be of rheumatological aetiology, it is mentioned that a missed infection or even medication could be an occult trigger [35,36]. Here is a brief summary of these case series.

- A retrospective case series review of MAS and systemic juvenile

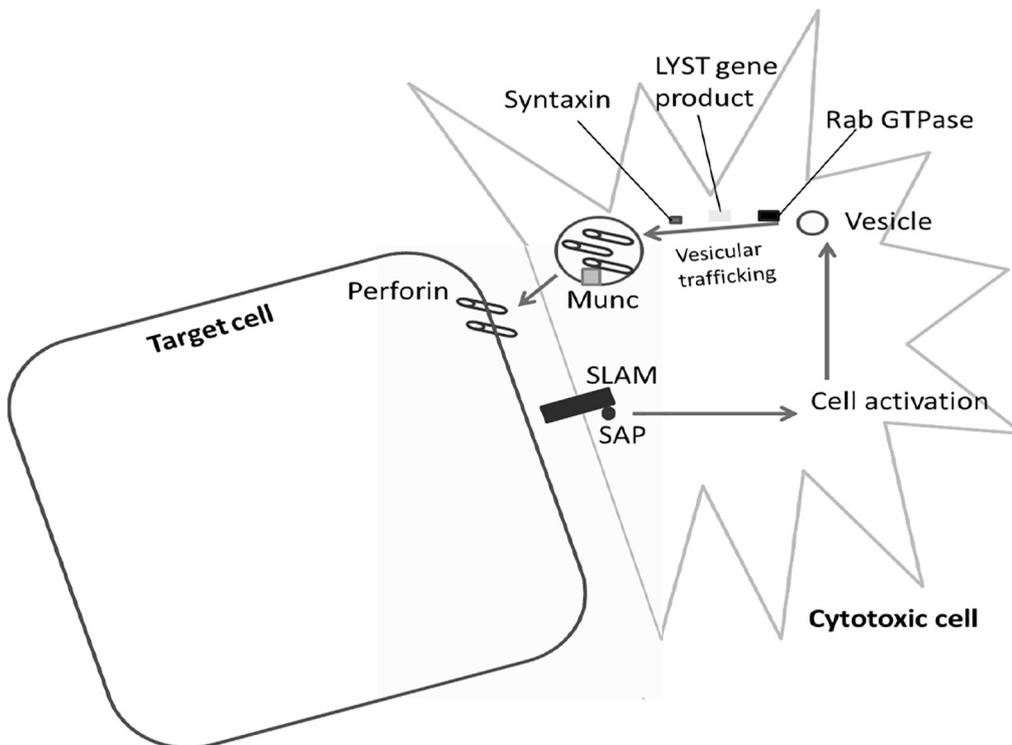
idiopathic arthritis revealed that over 80% of the 31 cases had a prior infection [37].

- A systematic review of macrophage activation syndrome in inflammatory bowel disease demonstrated that 98% of the 50 cases reviewed were caused by infection or malignancy [38].
- A retrospective review of cases of MAS from a database of children with rheumatic diseases found eight out of the nine cases were precipitated by infection [36].
- A retrospective study found 24 cases of MAS in inflammatory childhood diseases. 88% of the cases could be attributed to infection [27].

It is easy to incorrectly implicate inflammation on its own as the trigger for HLH. Infection, cancer and rheumatological conditions are all inflammatory and are associated with HLH. Mechanistically, this is too vague and the proposed model describes the pathophysiology in more detail.

*Adult onset Stills Disease*

Another important rheumatological disease that triggers UHH is Adult onset Stills Disease (ASD). This condition could be a thorn in the side of this theory as it causes hyperferritinaemia but is not an intracellular disease.



**Fig. 2.** The commonest defective proteins associated with F-HLH and how they are all involved in cytotoxic activity. PRF gene encodes for perforin protein which is secreted by cytotoxic cells and perforates its target cell. PRF mutations are found in 20–40% of F-HLH [27]. UNC13D codes for munc required for cytolytic granule exocytosis. Mutation found in UNC13D cause 10–20% of F-HLH [27]. STX11 gene encodes for syntaxin 11, which is postulated to play a role in intracellular trafficking and mutations and causes 10–20% of F-HLH [27]. 60–70% of mutations in X-linked lymphoproliferative syndrome are SAP gene mutation products which act as secondary messengers for signalling lymphocytic activation molecule (SLAM). SLAM goes on to activate cytotoxic T cells which attack target cells [27]. X linked lymphoproliferative syndrome is often associated with F-HLH. Lysosomal trafficking regulator gene (LYST-gene) products are linked to Chediak-Higashi syndrome, which is also associated with F-HLH. Its protein is involved in vesicular trafficking, which is fundamental in exocytosis and attacking target cells [27].

Mutations of RAB27a which produce Rab GTPase and is involved in protein transport. RAB27a mutations are found in Griscelli syndrome type 2, which is also associated with F-HLH [27].

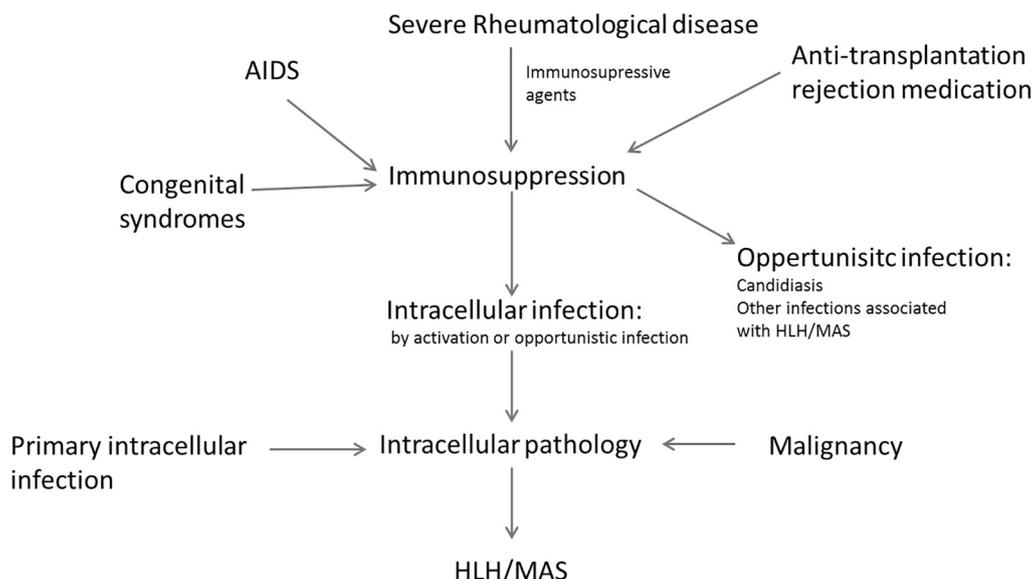


Fig. 3. A diagram demonstrating the possible cause and effect relationship of HLH triggers.

Table 3

Comparison of Yamagushi’s and Fautrel’s diagnostic criteria for ASD and HLH 2004 diagnostic criteria for HLH.

Yamagushi’s criteria [39]	Fautrel’s criteria [40]	HLH 2004 criteria [27] in bold and comments are in italics
Major criteria Fever > 39 for 1 week or more Arthralgia or arthritis lasting 2 weeks or more Typical rash Leucocytosis. Mostly polymorphonuclear cells	Major criteria Fever > 39 for 1 week or more Arthralgia Transient erythema > 80% polymorphonuclear cells	<b>Fever. Duration &gt; 7 days, peaks ≥ 38.5 C</b>  <i>A rash is present in a third of cases Often found in HLH</i>
Minor criteria Sore throat Lymphadenopathy Hepatomegaly or splenomegaly Abnormal liver function tests Negative tests for antinuclear antibodies and rheumatoid factor	Minor criteria Pharyngitis  Glycosylated ferritin less than 20% Maculopapular rash Leucocytosis	<i>Lymphadenopathy is very common in HLH</i> <b>Splenomegaly</b> <i>Abnormal Liver function tests are typical HLH are also negative for antinuclear antibodies and rheumatoid factor</i>  <i>A maculopapular rash is present in a third of cases Leucocytosis Often found in HLH</i>

\*One study examining ferritin glycosylation demonstrated that in HLH cases most ferritin levels were below 20% and all cases had ferritins below 25% [41].

One could, however, view ASD as a variant of HLH and if that were true then the proposed idea could still stand. But how likely is this? Review the Yamagushi’s and Fautrel’s [39,40] diagnostic criteria in Table 3, which are commonly used to diagnose ASD and compare it to the HLH 2004 Criteria. Only arthralgia is typical in ASD and not in HLH and the pharyngitis could be the source of an intracellular infection that precipitates these conditions. Comparing the diagnostic criteria of ASD and HLH therefore, informs us that there is a strong possibility that they might be the same disease.

More evidence is that that ASD is known to trigger MAS. Remember, we argue that MAS is another name for HLH, used when a rheumatological disease is associated. Another persuasive feature of ASD is the associated polymorphisms of the macrophage migratory inhibitory factor [42] which is involved, like F-HLH, in macrophage phagocytosis and cell to cell adhesion [43]. Finally, ASD is often triggered by the same viruses and bacteria that trigger HLH [44]. There should be enough evidence to at least consider ASD a variant of HLH.

The model’s predictions

Richard Feynman, Nobel laureate in physics, once said, “It doesn’t matter how beautiful your theory is, if it doesn’t agree with experiment, its wrong.” So, what predictions does this model make that could be tested in the future?

- Intravenous ferritin infusions may have a clinically beneficial effect on sepsis, cancer or severe inflammatory disease if ferritins’ antibacterial, antiangiogenic and immunomodulatory actions, respectively, are correct.
- Rheumatological disease do not trigger HLH.
- Extracellular pathogens are not causes of HLH. Specifically, candida and Fusobacterium infection are not triggers of HLH.
- Severe mitochondrial insult should be found in haemophagocytic macrophages in HLH cases.
- A drug that inhibits macrophage fusion might reduce hyperferritinaemia in animal models of HLH. It would be difficult to predict what clinical outcome this would have.
- A serum test for hybrid fusion cells could be designed to test for hybrid cells with macrophage and epithelial immunohistochemistry.
- Outside the context of haemochromatosis, UHH probably means that a severe infection or metastatic cancer is inflicting the patient. Both these conditions, if unknown, are of paramount clinical significance.
- There must be a mechanism that describes mitochondrial damage, an acquired reduction in oxidative phosphorylation with haem degradation and ferritin secretion by macrophages.

## Conclusions

This paper proposes a new theory of the pathophysiology of UHH, HLH and MAS. These conditions could be described as being on a continuum, with hyperferritinaemia at its mild end and life-threatening HLH at the other. Perhaps in the future UHH will be seen as a mild form of HLH not requiring treatment.

The theory would benefit from review by experts in the fields of haematology, infectious diseases, oncology, rheumatology and cell biology. The mechanism suggested attempts to piece together many observed aspects of hyperferritinaemia and HLH and some of the latest concepts trending in the literature. These concepts include the metabolic theory of cancer, the metastatic origins of cancer and the study of mitochondriopathies.

There is no doubt that this mechanism needs additional research, such as into the basic question of how toxic mitochondria triggers macrophage machinery to upregulate iron metabolism and hyperferritinaemia. If this research has already been done, it remains elusive in the literature. Also, the predictions outlined in this paper could be a rich source for future research in this field.

It would be hubris to think that this theory is complete or error-free. Novel ideas are delivered to the world raw and either moulded to fit scientific rigour or rejected outright. Moreover, in attempting to answer the three questions posed at the beginning of this paper (what is the purpose of serum ferritin, what controls UHH and whether it is increased in inflammatory disease) gave rise to a more fundamental question: is hyperferritinaemia a defence response rather than a disease?

## Conflict of interest statement

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