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FERRITIN AND ITS SIGNIFICANCE IN LEUCOCYTE

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ABSTRACT

The ubiquitous distribution of ferritin in virtually all cell types makes it play the central role in iron metabolism. In human leucocytes, both biochemical and physiological mechanisms involved in cell-mediated immune response have been linked positively with this protein. The small amount of ferritin generally present in normal leucotytes is found to be increased in patients with haematological malignancies accompanied by an increase in circulating ferritin. This high concentration is caused by release of ferritin into the serum from leucocytes synthesizing elevated amounts of the protein. The presence of ferritin on a subpopulation of peripheral blood lymphocytes of cancer patients results in a variety of immunosuppressive effects normally found in these patients. An increased lymphocyte-bound ferritin corresponds to development of malignancy with potential diagnostic and prognostic values. In addition, ferritin derived from the cells may have other important roles including the regulation of haemopoietic progenitor cell proliferation and differentiation.

INTRODUCTION

Ferritin is generally regarded as an iron storage protein, the small concentration of ferritin normally present in circulation reflecting the amount of storage iron in the boby. It is known that iron and its transport and storage proteins, namely, transferrin, lactoferrin and ferritin, are associated with the major sets of cells of the immune system, and may be involved in many immunological functions. Some effects may be linked to cells' requirement of iron for their metabolic activity, others may participate in still-unknown cellular mechanisms. In this review, I shall discuss some of the ferritin functions in leucocyte, in particular its significance in the cell, its regulation of cell immunity and proliferation, and the role of ferritin on the cell surface.

INTRACELLULAR FERRITIN

In various populations of peripheral blood leucocytes, the appearance of stainable iron granules in monocytes and lymphocytes from patients with haemochromatosis was the result of iron overload,[1,2] and measurement of ferritin in normal leucocytes showed no difference in leucocyte ferritin concentration between males and females.[3] However, within a population of leucocytes, monocytes contain a greater amount of ferritin than lymphocytes and polymorphs. Incubation of white blood cells from normal subjects and patients with acute myeloblastic leukaemia with ^{14}C-leucine demonstrated increased ferritin synthesis in the leukaemic cells compared to normal leucocytes.[4] Although ferritin synthesis in normal and in patients' leucocytes did not seem to be stimulated by increasing concentration of iron, it was suggested that ferritin protein in the leukaemic cells has the characteristics of apoferritin with a very low iron content and may be a specific leucocyte ferritin.[4] In addition, measuring of total protein and ferritin synthesis showed that while ferritin synthesis is probably sensitive to iron concentration in all cell types, this is most obvious in the case of monocytes, whereas the capacity of lymphocytes and polymorphs to respond in this way is limited.[3] Later, Lipschitz *et al.*[5] demonstrated that changes in leucocyte ferritin content reflected variation in iron stores, both in iron deficient and iron overloaded patients. Their findings are comparable with those of other investigators[6] who showed that the mean serum iron concentration was related to the mean leucocyte ferritin content in normal subjects and iron deficient patients.

It seems likely that human leucocytes contain a very wide range of isoferritins and ferritin concentrations. The measurement of ferritin by conventional assay either with anti-spleen ferritin antibodies[7,8] or anti-heart ferritin antibodies[9] may have led to underestimations. Experiments using both anti-spleen ferritin and anti-heart ferritin antibodies to measure ferritin contents in normal leucocytes showed approximately twice as much heart type as spleen type ferritin in monocytes and lymphocytes, but polymorphs had about twice as much spleen type as heart type ferritin.[10] The presence of isoferritins of differing isoelectric points in leucocyte extracts was also confirmed by anion-exchange chromatography. Many investigators demonstrated a good correlation between the affinity of ferritin for anion-exchange chromatography and subunit compositions. They found that anti-spleen reacting ferritin is relatively basic and should therefore contain a high proportion of L subunits and that anti-heart reacting ferritin, being more acidic, should contain a higher proportion of H subunit. The presence of these two types of ferritin subunit in leucocytes was also confirmed directly by incorporation of ^{3}H-leucine into these two ferritin subunits.[10,11]

It is known that the raised concentrations of ferritin found in serum from patients with leukaemia and Hodgkin's disease are associated with increased concentrations of ferritin in circulating leucocytes.[12-15] It is suggested that this high concentration is due to increased synthesis of ferritin by malignant cells with subsequent release of ferritin into the serum,[13] as there was a high proportion of serum ferritin bound to concanavalin A, suggesting that the secreted ferritin is glycosylated.[16] In addition, Dorner *et al.*[17] studied the synthesis and

secretion of ferritin in selected T and non-T lymphocytes from normal peripheral blood and from the spleen of Hodgkin's disease patients and found that T-lymphocytes synthesised and secreted ferritin molecules with a high proportion of H subunits. Using a haemolytic plaque-forming assay, de Sousa *et at.*[18]and da Silva *et al.*[19] were able to provide evidence of ferritin secretion from leucocytes. They found that ferritin secretion was more pronounced in mitogen-stimulated leucocytes than in non-stimulated cells. Recently, using incubation of leucocytes without addition of iron to the incubation medium, Worwood *et al.*[20] found increased ferritin concentration in the cells with preferential accumulation of acidic isoferritins; iron supplementation increased the ferritin concentration and this accumulation appeared to take place largely in monocytes. They also showed that there were small amounts of both spleen and heart type ferritin released during incubation of leucocytes in an iron-containing medium or following phagocytosis of red blood cells. Some concanavalin A-binding ferritin was also released into the medium suggesting that a fraction of the ferritin is glycosylated before secretion. Studies on the release of ferritin from lymphocytes stimulated with mitogen showed that the secretion of ferritin, as determined by concanavalin A-binding assay, increased with time, but the levels were lower than the intracellular concentration.[21] Confirmation of the presence of secreted ferritin from proliferative cells was obtained by anion exchange affinity chromatography.[21]

REGULATION OF CELL IMMUNITY AND PROLIFERATION

Apart from the central role of ferritin in iron metabolism, a number of physiological functions have been suggested for ferritin since the protein was first described by Laufberger in 1937.[22] It has been described as a vasodepressor material by measurements on the rat mesoappendix using a bioassay method.[23] Injection of this vasodepressor material extracted from liver into dogs showed a 70 to 80% reduction in urine flow, and the authors suggested this was due to stimulation of the neurohypophysis to secretion of its antidiuretic hormone.[24] Later, they showed that this antidiuretic active vasodepressor material present in liver is ferritin.[25]

It is generally accepted that the immune response is depressed in patients with malignant diseases, as this is reflected in impaired skin test, impaired reactivity to antigens and decreased T-lymphocyte counts as measured by rosette formation with sheep red blood cells.[26-28] This impairment has been attributed to the presence of a tumour-specific substance in the patients' sera.[29-31] The suggested presence of this tumour-related substance is based on the evidence that the depression of sheep erythrocyte rosette forming cells can be abrogated by treatment of the patients'lymphocytes with mild proteolytic enzymes.[28,30] *In vitro* treatment of these ferritin-bearing lymphocytes with papain, or with normal peripheral blood lymphocytes, or with an immunomodulator drug levamisole, resulted in shedding of the surface ferritin with a subsequent restoration of the sheep red blood cell rosetting capacity of the lymphocytes.[28,32-34] The restored T-cell subpopulation could again be inhibited by reincubation with the patients' sera[35] or by treatment with adenosine.[36] Adenosine has been shown to inhibit normal human lymphocyte response to

phytohaemagglutinin.[37] In a later finding, Moroz and Kupfer[38] showed that separation of the ferritin-bearing lymphocytes from the sheep erythrocyte-rosetting T-cells resulted in increased reactivity of the patients' T-cells in mixed lymphocyte cultures, and that readdition of the fraction containing the ferritin-positive cells to a mixed lymphocyte culture decreased the proliferative response of the patients' T-cells. They suggested that ferritin-positive T-lymphocytes in malignant patients' represent an active suppressor cell subset with a consequent decreasing of the patients' T-cells reactivity to alloantigens.

Matzner *et al.*[39] showed that splenic ferritin, obtained from thalassaemic patients, suppressed normal T-lymphocyte functions *in vitro.* The suppressive effects of ferritin include inhibition of concanavalin A and phytohaemagglutinin-induced lymphocyte blastogenesis, but has no effect on pokeweed mitogen-induced transformation. Recently, these workers have looked at the relative suppressive effects of various isoferritins, isolated from human term-placenta, on certain T-lymphocyte functions, and have shown that the basic isoferritins had no suppressive effect on phytohaemagglutinin-induced lymphocyte blastogenesis but showed a suppressive potential when concanavalin A was used. In contrast, acidic isoferritins suppress lymphocyte transformation induced by both mitogens, and their effect on concanavalin A-induced blastogenesis is somewhat more pronounced than that of the basic isoferritins.[40] Supportive evidence has shown that there is more heart type ferritin accumulation than spleen type ferritin accumulation in lymphocytes stimulated with mitogen.[21] This phenomenon is followed by an increase in ferritin synthesis.[41] Although the precise mechanism of ferritin expression in proliferative cell is presently unknown, it does, however, indicate a close relationship between increased ferritin synthesis and metabolic activity of the cells.[41] It also suggests that ferritin, particularly acidic ferritin which is often found in malignancy, might play a role in the development of abnormal T-cell function encountered in certain proliferative disorder.[40]

There is a considerable amount of evidence produced by Broxmeyer and colleagues suggesting that acidic isoferritins derived from monocytes or macrophages have a specific role in the regulation of haemopoietic progenitor cell proliferation and differentiation *in vitro*[42-44] and they have suggested that these proteins have a role in the pathogenesis of leukaemia. The original observation[45] described the presence of an inhibitory activity in the extracts and conditioned medium derived from bone marrow or blood cells of patients with acute leukaemia against colony formation by normal granulocyte-macrophage progenitor (CFUGM). This leukaemia-associated inhibitory activity (LIA) derived from non-adherent, non-phagocytic, low density, human Ia-antigen negative population of non-T, non-B lymphocytes with Fc receptors was identified as a heat-stable high molecular weight protein, which binds to concanavalin A-Sepharose and has an isoelectric point of about 4.7.[46,47] They also demonstrated that there is an increased release of acidic isoferritin inhibitory activity (AIFIA) from leukaemic cells which are Ia-antigen negative.[43] There are various factors, which modulate the release of AIFIA from normal monocytes and macrophages, such as T helper-lymphocytes which induce the release of AIFIA, but T suppressor-lymphocytes have the inverse effect.[44]

The apparent similarity of these physical characteristics to those of acidic isoferritins together with the detection of ferritin in LIA preparations and the detection of LIA in all ferritin preparations led Broxmeyer *et al.*[46] to name the acidic isoferritins as LIA. Their conclusion was based on the criteria that the LIA present in all cell extract preparations was inactivated by antiserum specific for acidic isoferritins and not by antiserum specific for basic isoferritins. More recently, it has been shown that LIA was inactivated by monoclonal antibody 2A4 against acidic isoferritin and H-subunits of ferritin molecules.[48,49] However, there are some inconsistencies in this hypothesis, as the composition of ferritin preparation previously described as inhibitory factor to CFU-GM colony growth[45] could not be confirmed in later study and they were not found to be predominantly acidic in nature.[50] Jacobs[51] pointed out that the difference in isoelectric points, subunit composition, immunoreactivity, glycosylation of ferritin and isoferritins from different sources may have different inhibitory activity for haemopoietic progenitor cells. Further investigations are needed to solve this problem.

LEUCOCYTE SURFACE FERRITIN AND ITS SIGNIFICANCE

Following Moroz *et al.'s*[33,34] description of a subpopulation of lymphocytes from peripheral blood of patients with breast cancer or Hodgkin's disease which bear ferritin on their surface, many studies have been carried out to investigate the potential diagnostic and prognostic value of these ferritin-bearing lymphocytes. Using antibody-dependent complement mediated cytotoxicity techniques to measure ferritin bound to the surface of lymphocyte in patients undergoing excision biopsy for suspected breast cancer, it has been shown that 45 of 47 blood samples from patients with stage I and II breast cancer, and in 20 of 22 patients with stage III disease were ferritin-positive but patients with benign breast disease, and samples from control women were negative.[52] More recently, Moroz *et al.*[53] developed the ferritin-bearing lymphocyte test further by using monoclonal antibody specific for oncofoetal ferritin, obtaining results similar to their previous report.[52]

Bluestein *et al.*[54] have evaluated a radioimmunoassay designed to determine ferritin bound to isolated peripheral blood lymphocytes. Using the mean percentage of specific binding of ^{125}I-labelled rabbit anti-Hodgkin's disease spleen ferritin antibody (%SP), they found the mean %SP for the non-cancer control group was in the range of 4.3 to 5.1 (n = 187), which was identical to that for inactive cancer or post-operative remission cancer group. Using a %SP normal cut-off level of 6.5, they were able to discriminate with a high degree of specificity and sensitivity between individuals with primary cancer and advanced cancer. Papenhausen *et al.*[55] have developed a simple indirect immunofluorescence technique for examining the number of ferritin-bearing lymphocyte in 44 patients with carcinoma of head-neck,colon and lung. They found that patients with cancer had a mean percentage of 10.0 $\pm$ 0.94 ferritin-positive lymphocytes in peripheral blood, whereas, there was only 3.1 $\pm$ 0.56% in the 25 control normal subjects.

In normal peripheral blood, Cragg *et al.*[56] used flow cytometry together with double immunofluorescence to define spleen ferritin distribution on the surface of leucocyte cells in order to explore its possible role in lymphocyte and macrophage functions. They found that 66% of monocytes and 75% of B-lymphocytes demonstrated positive results, but less than 10% of OKT3 (T-lymphocyte) were ferritin positive. Differentiation of helper and suppressor T-lymphocytes using OKT4 and OKT8 showed a minor fraction of both T-cell subsets to have surface ferritin. They suggested that the detectable presence of ferritin on the B-cell surface membrane, but only on a small fraction of T-cells, can not be attributed to differences in endogenous production, as T-cells from peripheral blood or spleen cells of patients with Hodgkin's disease synthesised greater amount of ferritin than B-cells.[17] However, the failure of T-cells to acquire surface ferritin in subjects with high serum ferritin suggests that the protein does not bind non-specifically[33,34] and that although the origin of B-cell surface ferritin is presently unknown, its presence is compatible with the suggestion that it determines lymphocyte distribution within the body.[18] However, it is still not clear whether ferritin present on the surface of lymphocytes in cancer patients is a specific binding of ferritin to cell surface associated with a high circulating ferritin concentration, or whether it has a more specific significance. Study using fluorescence activated cell sorter showed that phytohaemagglutinin caused a marked increase in the number of cells bearing ferritin on their membrane, whereas no such change occurs in non-stimulated cells. This coincides with increases in proliferative markers, including interleukin-2 receptor, transferrin receptors and HLA-DR antigens.[57] Although flow cytometric studies of T-lymphocytes in cancer patients showed that the number of cell bearing ferritin on their surface was significantly greater than normal, no difference in the number of interleukin 2 receptor or transferrin receptor-positive T-cells can be demonstrated among cancer patients and normal subjects,[58] suggesting that the presence of ferritin on the cell surface is not compatible to that seen in mitogen-stimulated T-cells where levels are 5 to 6 times higher than normal.[57] From a study on T-lymphocyte-bearing surface ferritin in 15 patients with newly diagnosed breast cancer by the same double fluorescence labelling techniques, Jacobs *et al.*[59] found that only 1 out of 8 patients with stage I/III disease had an increased level of ferritin-positive T-cells, but 4 out of 7 patients with stage IV disease had an increased number. A similar study was also carried out in patients with Hodgkin's disease, showing no change in the number of ferritin-positive B-lymphocytes and monocytes, but a significant increase in the percentage of T-cells bearing surface ferritin. However, no correlation between the presence of ferritin-bearing lymphocytes and disease stage was demonstrated. Similar results have also been reported in patients with squamous carcinoma of head and neck.[55] These results suggest that although the T-lymphocyte abnormality may be related to the stage of disease, ferritin-bearing lymphocyte assays can not discriminate the clinical stage of malignant disease. Supportive evidence in this part come from the study of Pattanapanyasat *et al.*[58] who found that the number of peripheral blood from breast cancer patients bearing ferritin on their surface is significantly greater than normal and that the number of ferritin-bound cells does not appear to be related to the clinical stage of the disease nor to the serum ferritin concentration, though this is higher in patients than in normal subjects.

However, the level of ferritin-bearing lymphocytes in cancer patients may prove of importance in the manipulation of cancer treatment. Study on the change in the number of ferritin-bearing lymphocytes in pre-operative and post-operative breast cancer patients showed that the numbers tended to be decreased after surgical removal of tumours and increased on recurrence of the cancer or appearance of metastases.[53] It is well known that elevated levels of serum ferritin have been reported in many malignant diseases[60] and that the source of the ferritin present in the serum is thought to be from the tumour tissues.[4, 13, 61] It is possible that the high concentration of ferritin, normally found in the serum of cancer patients, coating a subpopulation of circulating lymphocytes, may activate their suppressor cell activity. The activated suppressor cells may ultimately be responsible for the decrease in cellular-mediated immunity as shown by many investigators.[33,34,39,40] Recent studies revealed that there is no correlation between the levels of lymphocyte surface ferritin and serum ferritin levels in the patients, and that no elevation of lymphocyte surface ferritin was seen in patients with rheumatoid arthritis, haemochromatosis and bacterial infection.[62] More recently, Koprivova *et al.*[63] also confirmed that a high proportion of ferritin-positive lymphocytes was not always accompanied by high serum ferritin levels found in patients with Hodgkin's disease. These results suggest that the high number of ferritin-bearing lymphocytes cannot be explained by a specific binding due to the presence of high serum ferritin and therefore, the passive adsorption of ferritin from the blood by lymphocyte is unlikely to be true.

At present, although the function of ferritin-bearing T-lymphocytes is unknown, the presence of ferritin on the cell surface appears to be associated with malignancy and it may prove to be useful as a diagnostic and prognostic tool, or as a means of identifying patients at risk from developing cancer.

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บทคัดย่อ

เฟอริติน ซึ่งพบได้ทั่วไปในเซลเกือบทุกชนิด มีบทบาทสำคัญต่อ เซลเม็ดโลหิตขาว ในเรื่องของภูมิต้านทาน ปริมาณของ เฟอริติน ซึ่งตามปกติมีเล็กน้อยในเม็ดโลหิตขาวนั้น พบว่าจะมีปริมาณสูงขึ้นใน เซล ของผู้ป่วยมะเร็ง ของโลหิต ซึ่งผู้ป่วยเหล่านี้มักมี เฟอริติน สูงในกระแสโลหิต การที่มีโปรตีนชนิดนี้สูงในกระแสโลหิต เชื่อว่าเกิดจาก การที่ เซลมะเร็งมีการสังเคราะห์ เฟอริติน ที่เพิ่มสูงขึ้น ทำให้มีการหลั่งของ โปรตีน เฟอริติน ออกมายังกระแสโลหิต เป็นเหตุให้มี เฟอริติน บนผิวเซล ลิย์มโฟศัยท์ สูงขึ้นตามปริมาณและการสังเคราะห์ภายในเซลด้วย ปรากฏการณ์ที่มี เฟอริติน บนผิวเซล ลิย์มโฟศัยท์ นั้น นอกจากจะทำให้เกิดภาวะภูมิต้านทานพร่องในผู้ป่วยมะเร็งแล้ว ยังพบว่ามีความ สัมพันธ์กับการดำเนินการของโรค ทั้งในแง่การวิเคราะห์และการพยากรณ์โรคด้วย นอกจากบทบาทดังกล่าว เฟอริติน ยังมีส่วนในการควบคุมการงอกขยายและการเปลี่ยนแปลงของเซลตัวอ่อนของเม็ดโลหิตชนิดต่าง ๆ ของร่างกายอีกด้วย