Artykuł przeglądowy ***Review***

Haemosiderin-laden macrophages (HLMs): Current understanding and clinical relevance

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Summary

Tumour-associated macrophages (TAMs) are key components of the tumour microenvironment, playing a significant role in tumour progression. There are two main types of macrophages: M1 and M2, which differ in their activation mechanisms and functions. M1 macrophages are involved in the inflammatory and anti-tumour response, while M2 macrophages play a key role in regulating the inflammatory response, tissue repair and promote tumour growth, including angiogenesis and facilitating tumour cell migration. TAMs play a key role in tumour metastasist through a variety of mechanisms. In addition, macrophages, including haemosiderin-laden macrophages (HLMs), are involved in iron management in the body. Depending on their polarity, HLMs can sequester iron (M1) or release it (M2), which affects tumour growth. HLMs have been studied in various non-cancerous and cancerous processes in humans and animals. Their role has been the subject of numerous studies, but their impact on cancer development is still not fully understood.

Keywords: HLMs, macrophages, hemosiderin, neoplasm, TAMs

Tumour-associated macrophages (TAMs) are one of the cells present in the tumour microenvironment (TME) (10). They can be divided into two polarity types, M1 and M2. M1 macrophages are those activated by the classical pathway. Their main function is to help fight infection and induce inflammation (2). Polarisation in this direction occurs under the influence of pro-inflammatory cytokines (e.g. IFN-γ, TNF-α) and immunostimulatory cytokines (e.g. IL-12). In tumourigenesis, M1 macrophages are usually found early in tumour development and in well-vascularized regions of the tumour (6, 53). M2 macrophages are activated in an alternative manner. M2 macrophages are polarized under the influence of anti-inflammatory cytokines (IL-4, IL-10 and IL-13) (20, 60). These types of macrophages promote tumour growth by increasing angiogenesis, facilitating the movement of metastatic cells and weakening the host immune response against tumour cells (6, 47, 53). It is worth noting that macrophage polarization is a dynamic process that can shift from the M1 to the M2 phenotype or conversely, from M2 to M1, depending on environmental conditions (26).

TAMs are also involved in the metastatic processes of the tumours (10). This has been shown to occur at several stages, such as:

- the promotion of cell invasion into surrounding tissues, by influencing the epithelial-mesenchymal transition (EMT) process (13, 54);
- the promotion of tumor area vascularization, by secreting e.g. vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) (5, 36);
- the facilitation of tumor cells to enter the vascular lumen by releasing cathepsins, which damage the extracellular matrix (ECM) in the endothelial region, and by concomitantly releasing endothelial growth factor (EGF), which promotes tumour cell migration (57, 59);
- the assistance in egress of the tumour cell from the blood vessel (46);
- the preparation of a site for a metastatic cell in another organ by creating so-called pre-metastatic niches (PMN), by secreting factors such as chemokine (C-C motif) ligand 2 (CCL2), colony stimulating factor 1 (CSF-1) or tissue inhibitor of metallopeptidase (TIMP)-1, among others (25, 50).

Macrophages, including TAMs, are involved in the iron management in the body. They are responsible for recovering iron, mainly from aging erythrocytes. To a lesser extent, iron is also recovered from damaged tissue (15, 16, 48). Macrophages store and transport iron by accumulating it in the form of ‚aggregates of ferritin granules' called haemosiderin. These types of cells are called haemosiderin-laden macrophages (HLMs). Historically, these cells were called siderophages and when present in the alveoli, they were called heart failure cells (31). The presence of haemosiderin deposition in human tumours has been repeatedly studied and described in human medicine, although its effect on tumour development has not been clearly established (8, 21, 28, 33, 56).

It is worth noting that iron metabolism differs significantly between M1 and M2 macrophages (33). M1 polarised cells typically occur in response to pathogen invasion or during tumour development, these macrophages sequester iron to limit its availability for utilisation (26). In contrast, M2 macrophages exert anti-inflammatory effects and up regulate the expression of ferroportin, which results in increasing the export of cellular iron (12, 49). These results in increased iron availability within the tumour microenvironment (TME), and elevated iron concentrations can promote tumour progression (26).

The function and mechanisms in which HLMs are involved are poorly understood. The aim of the present review is to gather information regarding HLMs and their role in the body in humans and animals, in non-neoplastic lesions and in neoplastic lesions.

HLMs in human medicine – non-neoplastic lesions

In human medicine, HLMs have been studied and described in inflammatory processes (mainly in the lungs) and in neoplastic proliferations of the thyroid and mammary glands in women (3, 17, 24, 34, 41). There is also a publication describing HLM in the diagnosis of endometriosis in a woman (4).

Gaur et al. demonstrated the presence of HLMs in a case report of xanthogranulomatous pancreatitis, a rare type of pancreatitis that can mimic a malignant neoplastic process (17). It is likely that their presence was associated with foci of extravasated blood within the affected tissue. The authors did not show a correlation between the presence of HLMs and their effect on the development of the above tumours (17).

Bedaiwy et al. investigated that the presence of HLMs in peritoneal fluid could be used for diagnosing endometriosis in women (4). According to their results, the presence of HLMs has a low sensitivity of 52% but an acceptable specificity of 87% in diagnosing endometriosis. Based on their study, they hypothesized that the presence of HLMs in endometriosis may indicate abnormal iron metabolism within the peritoneum.

In diffuse alveolar haemorrhage (DAH), the diagnosis is made by determining the percentage of HLMs in the total number of macrophages in broncho alveo larlavage (BAL) sediment preparations (1, 19, 27, 32, 42, 44). According to Lassence et al. a finding of more than 20% HLMs allows the diagnosis of DAH, but does not definitively determine its cause (32). A different conclusion was reached by Maldonado et al. According to their study, DAH cannot be distinguished from diffuse alveolar damage (DAD) (37). Their results showed that an increased number of HLMs in BAL can be observed in patients with DAD and is not specific for DAH. In contrast, they observed that patients with ≥ 20% HLMs in BAL had a significantly worse prognosis than those with < 20% (37).

The results of the study by Priftis et al. demonstrated the presence of HLMs in BAL in patients who had received multiple blood transfusions, possibly indicating secondary pulmonary haemosiderosis (44). They also found a correlation between the number of HLMs in BAL and serum ferritin, suggesting that they could be used as indicators of pulmonary overload in patients requiring blood transfusion (44).

HLMs have also been observed in idiopathic pulmonary fibrosis (IPF) (29, 45). This entity is characterised by interstitial lungfibrosis, poor prognosis and limited response to treatment. Kim et al. found that lung iron deposition in the form of haemosiderin in IPF correlated with increased right ventricular systolic pressure (RVSP) measured by echocardiography (29).

Similar results were obtained by Fukihara et al. and Puxeddu et al. who assessed the percentage of HLMs in BAL from patients with IPF and additionally obtained its correlation with pulmonary vascular resistance (PVR) (14, 45). Puxeddu et al. carried out research on the following groups: 14 healthy people as control group (seven were current cigarette smokers and seven have never smoked) and 47 people with IPF (26 were ever-smokers and 21 were never-smokers) (45). Interestingly, IPF patients exhibited a significantly higher percentage of iron-containing alveolar macrophages than the control group. The specific results were as follows: 5.0% for non-smoking persons; 6.0% for healthy smokers; 29.0% for ever-smoking patients with IPF; and 36.9% for never-smoking patients with IPF. The results obtained for ever-smokers and never-smokers with IPF were impressively similar (45).

Exacerbations of chronic obstructive pulmonary disease (COPD) may be caused by an infectious agent or oxidative stress. In COPD most excess iron is stored in alveolar macrophages and airway epithelial cells in the form of insoluble haemosiderin complexes. The mechanism is intended to minimize oxidative damage caused by iron ions. In line with the observation of Mohan et al. it can be concluded that the amount of HLMs in BAL provides an estimate of the number of exacerbations over the past two years in patients with COPD (39). For every 1% increase in the amount of HLMs in sputum, there is a 4% increase in the number of infectious acute exacerbations COPD (AECOPD) cases (39). Unfortunately, it is not possible to conclusively determine whether the increased amount of HLMs is secondary to the underlying cause of AECOPD (e.g. infection) or is the primary infectious factor leading to AECOPD (39). HLMs have also been studied in relation to acute exacerbations (AE) in patients with various types of idiopathic interstitial pneumonia (IIP) (3). According to Arai et al. increased haemosiderin in lavage macrophages is a significant signal of AE-IIP, but does not predict the occurrence of AE (3). Patients with IIP who have elevated HLMs in BAL require regular monitoring of HLMs counts to prevent exacerbation of the disease processor to allow prompt medical intervention if it occurs (3).

HLMs in human medicine – neoplastic lesions

HLMs are not commonly studied cells in human medicine. To date, their presence has been studied and described in thyroid tumours and mammary tumours in women (24, 34, 41).

In a study of patterns of residual disease after neoadjuvant chemotherapy for breast cancer, Pastorello et al. showed that HLMs and free haemosiderin were deposited more frequently in the stroma of so-called triple-negative breast cancer (TNBC) tumours than in the stroma of tumours of other subtypes (41). Similar results were obtained by Lee et al. in their study (34). Both of the above-mentioned teams were unable to reach a conclusion on whether HLMs can influence metastatic lesions (34, 41).

HLMs have also been studied and described in the differentiation of benign follicular thyroid lesions from follicular thyroid neoplasms by Jaffar et al. (24). Nodular lesions of the thyroid can vary in nature and origin. The most commonly diagnosed lesion is considered to be a benign colloid nodule, which should be differentiated from follicular neoplasms (adenoma and carcinoma of the follicular or Hürthle cell type) and papillary thyroid carcinoma (58). According to their findings, with the exception of papillary thyroid carcinoma and Hürthle cell carcinoma, the finding of HLMs in fine-needle biopsy specimens indicates a benign colloid nodule-type lesion. The authors hypothesized that benign colloid nodules may have increased venous pressure compared with follicular thyroid tumours. This increased pressure would explain the presence of HLMs in colloid nodules on the same basis as bronchial lavage in patients with congestive heart failure. However, the authors emphasise that further research is needed in this area to establish diagnostically useful guidelines.

HLMs in veterinary medicine – non-neoplastic lesions

As in human medicine, HLMs in BAL have been studied extensively in cats and dogs with respiratory and cardiovascular disease (7, 11).

A study by Hooi et al. aimed to determine the frequency with which HLMs are observed in BAL in dogs and cats in the course of various lung diseases (22). The diagnosis of lung disease was based on fine-needle aspiration biopsy. In their study, the presence of HLMs was found in 13/171 (7.6%) samples from dogs and 18/34 (52.9%) samples from cats. According to the results, cats were significantly more likely to have pulmonary haemosiderosis. This may be due to the fact that cats have thinner blood vessel walls than dogs, which favours the occurrence of alveolar haemorrhages with pressure changes in the course of lung disease. In addition, the authors suggest that the slower clearance of HLMs from the lungs in cats than in dogs may also play a role. It is worth noting that the authors point out that the results may also have been influenced by the small number of cats included in the study. There was also no correlation between the age, sex or weight of the animal and the amount of HLMs observed in the lavage fluid. However, in the study mentioned above, it was found that dogs with lung cancer had higher levels of HLMs in the BAL. This is probably due to the fact that the neoplasm, as it grows, causes damage to the lung tissue leading to micro haemorrhages within the lung. It was also found that the highest percentage of pulmonary haemosiderosis was observed in inflammatory diseases of the lung. This may be due to the release of inflammatory cytokines which cause vasodilatation of blood vessels and increase erythrocyte diapedesis (55). In cats, haemosiderosisis most often seen with neutrophilic or mixed inflammation and is uncommon in cases with high eosinophilic inflammation. This is the opposite result to that obtained by DeHeer et al. who observed numerous HLMs in lavage specimens from cats diagnosed with asthma (11). This was probably due, as before, to the inclusion of too small a group of cats in the study.

HLMs in veterinary medicine – neoplastic lesions

There are not many research reports regarding HLMs in veterinary medicine. They have been described in malignant tumours of the mammary gland in bitches (18, 38).

Marques et al. investigated the presence of iron in macrophages in the lining of mammary tumours in dogs and cats (38). However, their study focused on the expression of iron-related proteins such as hepcidin, ferroportin 1 (FPN1), transferrin receptor protein 1 (TfR1) and ferritin (FT). According to their results, there are no statistically significant differences in the expression levels of iron-related proteins between benign and malignant tumours in dogs and cats.

Giambrone et al. in their study of mammary malignancies in bitches, focused on the characteristics of HLMs (18). They found that the number and location of HLMs varied according to the type of tumour. However, their number did not correlate with the degree of malignancy of the tumour examined. They also discovered that in the different subtypes of mammary cancer, the amount of HLMs showed statistical differences in the context of their total amount within the tumour and their amount only in the stroma of the tumour. In fact, HLMs were less common in the stroma of complex carcinomas. A limitation of the study was the small number of cases included. Therefore, the above conclusions should be considered carefully.

In the above studies, macrophages reacted strongly with an antibody against CD204. This protein, which is a receptor within the macrophage cell membrane, is highly expressed in M2 macrophages (30). It has been demonstrated in both human and veterinary medicine that a high proportion of CD204 (+) macrophages in TAMs is associated with a worse prognosis for the patient (23, 40, 43). Giambrone et al. also examined the expression of VEGF (vascular endothelial growth factor) and TGF-α (transforming growth factor α), among others (18). M2 polarised macrophages also showed a positive reaction with the above proteins. VEGF promotes angiogenesis, stimulates proliferation and increases vascular permeability (52). TGF-α is a protein with a mitogenic role for epithelial cells and fibroblasts. It also has an angiogenic effect (51). Based on the above information, the authors concluded that HLMs should be considered as polarized towards M2 macrophages. Thus, they promote the development of the tumour process by promoting angiogenesis and proliferation of the tumour cells (18).

However, a study by Leftin et al. (35) showed different results. In the case of implantable mammary tumours in mice, macrophages showed no polarization towards type M1 or M2. However, in metastasis the macrophages polarisation was noticeable. When the tumour metastasised to the lung, the macrophages became M2-polarised; but when it metastasised to the brain, the macrophages showed a polarity towards M1 macrophages. Based on their results, they hypothesized that the polarity of HLMs is more likely related to the tissue in which they are located than to the presence of iron deposits in these cells. It should be noted that the above study focused more on assessing the presence of HLMs *in vivo*, by quantitatively mapping them and determining their size and frequency of occurrence using magnetic resonance imaging (MRI).

HLMs, as a type of macrophage, are relatively poorly known in both human and veterinary medicine. So far, they have been considered as cells indicating the presence of haematopoiesis in non-neoplastic processes. However, their role in cancer deserves much more attention. Particularly, in the mammary gland tumours. Determining the dominance of either type according to their polarisation (M1 or M2 macrophages) in the primary and metastatic tumours as well as identification of factors stimulating polarisation, will make it possible to determine the role of HLMs in the primary tumour development and occurrence of the metastasis.

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