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Review Article

Metastatic Lymph Node Pathology

Ibtihal Mohammad Zabermawi*

Ministry of Health, Saudi Arabia

***Corresponding Author**: Ibtihal Mohammad Zabermawi, Ministry of Health, Saudi Arabia.

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Abstract

Background: Many cancers go through a progression that involves metastasis. This metastasis in many solid tumors begins with lymph node invasion. Many factors play an important role in the transformation of a primary tumor into a metastatic tumor. Due to the nature of the antitumor immune effects of the lymphatics, a primary step of metastasis involves immunosuppression. Some of these factors are extracellular vesicles and chemical factors like chemokines. Studies have also indicated that lymph node metastatic cells can be polyclonal which has many implications upon therapeutic strategies used against metastatic disease.

Aim of Study: In this article, our aim is to review metastatic lymph node pathology.

Methodology: A comprehensive and systematic search was conducted regarding metastatic lymph node biopsy. PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com) were the mainly used databases.

Conclusion: Lymph node metastasis is currently a crucial investigative arena in oncological research. Evidence continues to surface that supports a pivotal role for lymph nodes in the metastatic progression of many solid tumors. Thus, it is imperative that research is continued in this arena.

Keywords: *Lymph Node Metastasis; Cancers; Immune System*

Introduction

Cancer metastasis is a clinical challenge that leads to death. Cancer frequently metastasizes to lymph nodes and this is usually a predictor of increased mortality in most types of cancer. Since lymph nodes are important in the initiation of antitumor immune response, cancers that have spread to the lymph nodes must have escaped detection by the immune system. The mechanism of lymph node metastasis has many steps and regulators. The development of lymphangiogenesis and the preparation of a microenvironment suitable for cancer growth within lymph nodes is important for metastasis to occur. This is known as the premetastatic niche. It is only then that cancerous cells invade through the lymphatic vessels and move to the tumor-draining lymph nodes (TDLNs). In these metastatic lymph nodes, whether these cancer cells survive depends on how immunogenic they are, as well as the degree of immunosuppression within the lymph node. As in primary tumors, cancer cells affect the local microenvironment within the metastatic lymph nodes, making it more suitable for infiltration with a decreased reactivity of immune cells. This microenvironment within the lymph nodes determines the growth of the metastatic tumors as well as the response to medications. It has been shown that very few systemic medications actually accumulate within lymph nodes. Also, cancer cells within lymph node metastasis have been implicated in distant metastasis through the lymphatic or hematogenous route. Thus, it is imperative to develop therapies that target lymph node metastasis [1].

Methodology

A comprehensive and systematic search was conducted regarding metastatic lymph node biopsy. PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com) were the mainly used databases. All relevant available and accessible articles of all types were reviewed and included. The terms used in the search were lymph node biopsy, cancer, metastasis, pathology of lymph nodes.

Pathogenesis of lymph node metastasis

Physical factors, such as blood and lymphatic flow, and molecules expressed in the tumor microenvironment determine tumor cells' organ selectivity leading to metastasis. Evidence shows that lymph node metastasis not only gives prognostic indications but also has an active role in metastasis to distant organs and lethality. That said, our understanding of the molecular processes underlying this transformation is still developing. It is still under debate whether cancer cells are trapped by lymph nodes and thus slowing down cancer dissemination, if lymph node metastasis only indicates cancer cell transit through the lymph nodes, or if lymph nodes provide an environment that amplifies cancer cells and propagates systemic metastasis. Lymph node metastasis can be considered as a side part of the hematogenous metastatic loop due to the lymphatic and hematologic connections through the thoracic duct and lymphovascular shunts [2].

Extracellular vesicles (EVs)

Lymphatic vessels not only deliver cancer cells, but also primary tumor-derived soluble and vesicle-associated factors that make TDLNs more favorable for cancerous cell seeding. Exosomes are a type of extracellular vesicles that have been noted to affect immune and stromal responses within TDLNs. In one study where melanoma-derived exosomes were transfected into footpads and later followed by melanoma cell transfection, it was noted that the lymphatic vessels had a similar melanoma cell distribution pattern as the premetastatic melanoma-derived exosomes. This indicates that the metastasis of cancer cells to the lymph nodes is influenced by exosomes. Exosome injection upregulated genes associated with the recruitment, retention and development of lymph node metastasis. Which components within these exosomes (mRNA, miRNA, or proteins) is driving changes in lymph node gene expression is still unclear. Also, it has been shown that melanoma exosomes manipulate and mobilize bone marrow-derived cells to lymph nodes and other metastatic sites where they promote cancer cell invasion [3].

It has been shown in one study that in order to accelerate tumor development in macrophage depleted lymph nodes, tumor-derived extracellular vesicles (TeVs) must be released. CD169+ subcapsular sinus (SCS) macrophages trap TeVs in premetastatic lymph nodes and thus protect them from immunosuppression. However, precisely how these TeVs escape SCS macrophage trapping is still not understood. It can be surmised though that between the many complex interactions within premetastatic lymph nodes, extracellular vesicles promote an immune suppressed microenvironment that is necessary to lymph node metastasis [4].

Chemokines

Evidence suggests that the most inefficient stages of metastasis are the survival of the metastatic foci and their persistence after colonization. This points to the importance of the interaction between the cancer cell and the microenvironment. Many components affect tumor organ selectivity. The interaction between cancer cell chemokine receptors and their ligands on target organs has been shown to be very crucial [5]. Many chemokines and their receptors have been studied so far to be important in metastatic organ selectivity. An example of this is the CXCL12-CXCR4 interaction in breast cancer metastasis to the bone. Chemokines also play a role in lymph node metastasis. Studies have shown that CXCR3, CXCR4 and CCR7 are important players in lymph node metastasis. These chemokines are part of recruitment and patterning of immune cells to the lymph nodes. It is proposed that tumor cells will often acquire these chemokine receptors and are thus controlled very similarly to immune cells when interacting with their ligands [5,6].

CXCR3 has been shown to have an important part in lymph node metastasis of melanoma and colon cancer cells, but not in their hematogenous spread. A study in which B16F10 mouse melanoma cells with a decreased CXCR3 expression through antisense RNAs were subcutaneously inoculated in mice footpads found that the metastatic frequency of these cells to the popliteal lymph nodes was greatly decreased when compared with controls. No effect was detected on distant metastasis to the blood, lung or liver [7]. In another study, human colon cancer cells expressing CXCR3 cDNA (DLD-1-CXCR3) were rectally transplanted in nude mice resulting in macroscopic me-

tastasis to the paraaortic lymph nodes in 59% of mice; a dramatic increase from the 14% in control mice. CXCR3 did not seem to affect metastasis to the liver or lung [8].

In one study, the expression of CXCR3 was found in 33.7% of cases with lymph node metastasis. Also, a greatly decreased survival was noted in CXCR3-positive colon cancer when compared to those with CXCR3-negative status. Although CXCR4-positive cancers also had a poorer prognosis, the effect was less pronounced than that of CXCR3. Tumors positive for both CXCR3 and CXCR4 had the worst prognosis [8]. These results mimic those found in breast cancer where high CXCR3 expression was associated with a worsening prognosis. As such, the expression of CXCR3 promotes tumor metastasis to the draining lymph nodes, leading to a poorer prognosis. This also indicates that lymph node metastasis affects cancer patient survival.

Many studies have shown that CXCR3 plays an important role in the metastasis of many cancers including colon, breast, ovarian, prostate, melanoma, and neuroblastoma. Several studies indicate that CXCR3 enhances the invasion-related properties of tumors. It has also been shown that CXCR3 enhances the metastasis of breast, colon and lung cancers [9,10]. Also, lymphangiogenesis in sentinel lymph nodes is associated with distant metastasis. All this together suggests that chemokines and lymphangiogenesis that are parts of the lymph node microenvironment can propagate the metastasis of cancer cells to sentinel lymph nodes and other organs [11].

Clonality of lymph node metastasis

The chronological sequence of events that occur in cancer metastasis is a heavily researched and discussed topic. Some researchers have conducted lineage tracing and gene sequencing on primary and metastatic tumors in order to shed more light upon this topic. One study used a genetically engineered mouse model of small cell lung carcinoma to investigate the clonal evolution of cancer cells at metastatic sites like lymph nodes and liver. The model they used mimics human cancer by having lung-specific deletion of the tumor suppressor genes TP53 and RB1. This results in a progression from small neuroendocrine clusters in the lung into metastasis in lymph nodes and liver. The researchers then sequenced the genes of the primary tumor and the lymph node metastases. The results indicated that the lymph node metastatic cells were polyclonal arising from multiple primary tumor subclones [12].

Another group of researchers conducted a PCR-based study to reveal somatic variation in the hypermutable polyguanine (poly-G) repeats. This can be used to calculate the mitotic history and clonal composition in human tumors. The researchers found that poly-G variants existed in 91% of tumors and they constructed phylogenetic trees to elucidate the metastatic progression for each of the advanced colon cancer patients. The analysis uncovered varying degrees of intratumor heterogeneity between the patients. In two patients with distant metastasis to the ovary showed that the ovarian tumor was clonally separate from the primary colon tumor and lymph node metastasis, while the lymph node samples were identical to the primary tumor. This suggests that lymph node metastasis consists of polyclonal tumor cells. This means that using a single targeted therapeutic agent in the treatment of lymph node metastasis may be difficult. Also, if these cancerous cells were to exit the lymph nodes, distant sites would be seeded by multiple clones at the same time. Lastly, this could mean new mutations may be occurring in the lymph nodes that stimulate polyclonal distant metastases that are dissimilar to the primary tumor [13].

Conclusion

Research in the process of lymph node metastasis and how lymph nodes play a role in cancer progression has increased our understanding of their importance. Lymph node metastasis is preceded by alterations in the nodal microenvironment. A detailed comprehension of the molecular processes in the premetastatic lymph node microenvironment that lead to cancer metastasis may yield potential therapeutic targets to limit lymphatic metastasis. Due to the polyclonality of lymph node metastasis, it is not clear if a single targeted therapy would be curative. Similarly, to primary cancers, lymph node metastasis may acquire mechanisms to resist these therapeutics. In patients where the mechanism of drug resistance in the metastasis differs from that of the primary tumor therapeutic strategies may be

complicated. However, clinicians and researchers are becoming more aware that cancer cell proliferation and survival could be microenvironment specific, and more research is progressing in this field.

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