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Review

Giant cell tumor of bone: A basic science perspective

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ABSTRACT

Comprehending the pathogenesis of giant cell tumor of bone (GCT) is of critical importance for developing novel targeted treatments for this locally-aggressive primary bone tumor. GCT is characterized by the presence of large multinucleated osteoclast-like giant cells distributed amongst mononuclear spindle-like stromal cells and other monocytes. The giant cells are principally responsible for the extensive bone resorption by the tumor. However, the spindle-like stromal cells chiefly direct the pathology of the tumor by recruiting monocytes and promoting their fusion into giant cells. The stromal cells also enhance the resorptive ability of the giant cells. This review encompasses many of the attributes of GCT, including the process of giant cell formation and the mechanisms of bone resorption. The significance of the receptor activator of nuclear factor-κB ligand (RANKL) in the development of GCT and the importance of proteases, including numerous matrix metalloproteinases, are highlighted. The mesenchymal lineage of the stromal cells and the origin of the hematopoietic monocytes are also discussed. Several aspects of GCT that require further understanding, including the etiology of the tumor, the mechanisms of metastases, and the development of an appropriate animal model, are also considered. By exploring the current status of GCT research, this review accentuates the significant progress made in understanding the biology of the tumor, and discusses important areas for future investigation.

Contents

Introduction

Comprising approximately 6% of all primary bone tumors [1,2], giant cell tumor of bone (GCT) is a prominent lesion that presents with significant local osteolysis. Its name is derived from the numerous multinucleated giant cells found within the tumor, which are principally responsible for the extensive bone resorption that is characteristic of GCT. However, the neoplastic components of GCT are the spindle-like stromal cells, which promote giant cell formation and largely direct the pathogenesis of the tumor. The tumors arise predominantly in the epiphyses of long bones in the appendicular skeleton [2], but GCTs can occur in any other areas of the skeleton. Although locally aggressive, GCTs are most often benign, and only rarely metastasize to the lungs with a reported incidence rate ranging between 2 and 6% of cases [2–4]. Isolated reports have also detailed cases where GCT has metastasized to other locations, including the breast [5], heart [6], skin [7], and lymph nodes [8]. Surgical removal of the tumor is often the preferred treatment of GCT, although it is sometimes impractical or otherwise not desirable, and there is a recognized tendency for GCTs to locally recur in many cases following surgery [9–11]. Therefore other treatment options for GCT are continuously explored, and an understanding of the biology directing the pathogenesis of the tumor has already heralded new therapeutic options including bisphosphonates [12,13] and the monoclonal antibody denosumab [14]. Further understanding of the etiology and pathophysiology of the tumor may lead to other advancements in adjuvant or primary treatment options for patients

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with GCT. This review explores the current understanding of GCT, including the characteristics of each cell population and the mechanisms that direct its osteolytic phenotype. A commentary on the status of GCT research and perspectives for future research are also discussed.

Stromal cells

GCTs are heterogeneous tumors that are composed of several cell types. A defining feature of the lesion is the presence of numerous multinucleated giant cells that are uniformly distributed amongst mononuclear spindle-like stromal cells and other monocytes. As mentioned, the spindle-like stromal cells are actually the neoplastic component of the tumor, owing to their ability to readily proliferate in culture [15,16] and their capacity to form tumors in mice [17]. Indeed, high recurrence rates following surgical removal of the tumor may result from residual stromal cells that are capable of re-forming the tumor. In point of fact, a subpopulation of GCT stromal cells that express Stro-1 was reported to have stem-like properties [18]. Collectively, the stromal cells show positive expression of bone sialoprotein, osteonectin, osteopontin, osterix, and the runt-related transcription factor 2 (Runx2) [16,19–25], but only occasional expression of osteocalcin [19,20,23,24], which is often not detectable at the protein level [16,21–23], suggesting a mesenchymal lineage and pre-osteoblast phenotype. However, the stromal cells are themselves a heterogeneous population and may consist of cells at multiple stages of differentiation. For example, there are conflicting in vitro reports as to whether the stromal cells can further differentiate into mature osteoblasts upon stimulation [21,22,24,25], and one report that suggests the cells are differentiable not only into osteoblasts, but also into adipocytes and chondrocytes as well [16]. Nevertheless, within GCT, small areas of osteoid formation may be observed [1,26,27], although its presence is not characteristic of the tumor. Cultured stromal cells are able to form mineralized nodules following prolonged incubation [28], and are capable of stimulating bone formation when implanted subcutaneously in some [28,29], but not all [17], mouse models. Therefore, the lack of sufficient new bone formation within GCT may result from the preponderance of giant cells, which are bone-resorbing, osteoclast-like cells. Additionally, osteoclasts are able to suppress osteoblast differentiation [30], and media conditioned by giant cells from GCTs decrease collagen synthesis by osteoblastic cells [31]. Moreover, a recent report indicates that elimination of giant cells using denosumab results in new bone formation in treated patients [32].

Karyotype analyses of tumor samples have revealed that non-clonal chromosomal aberrations are a common feature of GCTs, including insertions, deletions, translocations, and other structural or numerical chromosomal rearrangements [27,33–36]. However, few clonal irregularities are detectable, although clonal alterations may be more prevalent in recurrent GCTs as opposed to non-recurrent cases [37], which may further indicate that tumor recurrence is possible from one or a few stromal cells. The most prevalent cytogenetic finding in GCTs is telomeric associations, where two different chromosome arms have fused together at their telomeric ends. These associations occur in more than 70% of cases [34,35], and are also present in isolated cultured stromal cells [38]. Given that the giant cells do not undergo mitosis [39], and genetic alterations were only observed in CD68-negative cells [37], which exclude monocytes, these alterations can be attributable to the spindle-like stromal cells. Several chromosome arms were reported to involve telomeric fusions more often than others, including 11p, 15p, 19q and 20q [27,33,35,36,40], although no predictable pattern has resulted from these analyses and their significance remains unknown. A reduction in telomere length may predispose certain chromosomes to these associations, which may, in turn, lead to additional chromosome aberrations [41]. Indeed, telomerase is also heterogeneously activated in these tumors [42,43]; further suggesting that telomere instability may participate in the development of GCTs. However, these cytogenetic abnormalities do not correlate with established clinical grading systems for GCTs [33], which suggests that a uniform genetic cause of the tumor is unlikely. In actuality, these instabilities may indicate that a variety of genetic aberrations may lead to a general tumor growth with a consistent clinical outcome.

Given these numerous genetic alterations, the status of the p53 tumor suppressor and other cell cycle regulators may also contribute to the progression of GCTs. Wu et al. [44] reported that p53 is commonly mutated in GCTs. In contrast, other analyses have suggested that p53 is typically not mutated in primary lesions [45–48], although there is evidence indicating mutations in stromal cell p53 may be correlated with local recurrence, malignant transformation, and metastasis of the tumor [37,49–55]. MDM2, which suppresses p53 activity by promoting its ubiquitination and subsequent degradation, is also often overexpressed in primary GCTs [16,45,50,56]. Moreover, the ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) gene is inactivated in GCTs [57], which may also contribute to destabilization of p53 and accumulation of MDM2 [58]. Together, these results suggest that the tumor suppressor functions of p53 may be insufficient in GCTs. Interestingly, the only reported spontaneous development of a GCT-like lesion in a mouse arose in a p53-deficient model [59]. However, the stromal cells express an alternatively-spliced MDM2 variant [56] that may promote neoplastic growth in a p53-independent manner [60]. Therefore, a comprehensive analysis of p53 and its associated proteins in GCT is necessary to provide further clarification on their contribution to the pathology of the tumor.

Giant cells

The giant cells are large multinucleated cells that exhibit many of the properties of osteoclasts. In fact, GCTs were formerly known as "osteoclastomas," and giant cells isolated from these tumors are often used as models for true osteoclasts [61–65]. Indeed, the giant cells express tartrate-resistant acid phosphatase (TRAP) [66,67], cathepsin K [61,68–70], and carbonic anhydrase II [64,71], as well as many receptors that are characteristic of osteoclasts, including the receptor activator of nuclear factor-κB (RANK) [72–74], the calcitonin receptor [75,76], and the αvβ3 integrin [71,77,78]. Moreover, the giant cells are capable of bone resorption [12,78–80] and may occasionally show numerous infoldings under electron microscopy that resemble the ruffled membrane of true osteoclasts [79,81]. Perhaps the most significant difference between these cells and other osteoclasts is that the giant cells can be considerably larger, containing hundreds of nuclei [1,82].

Giant cells are formed from hematopoietic precursors, and their synthesis is directed by the spindle-like stromal cells in a process that closely mirrors osteoclastogenesis. Namely, the stromal cells produce chemokines, including stromal cell-derived factor-1 (SDF-1) [83] and monocyte chemoattractant protein-1 (MCP-1) [84], that recruit monocytes to the tumor site. These monocytes are characteristically positive for CD68 expression [29,85], as well as variably positive for other macrophage lineage markers including HLA-DR, CD14, CD33, CD45, and CD51 [26,29,72,85,86]. The monocyte precursors, which may comprise approximately one third of the total mononuclear cell population [84], are thought to originate from the vasculature. Indeed, GCTs are often hypervascularized [87,88], and vascular endothelial growth factor (VEGF) expression is elevated in clinically aggressive cases of the tumor [89,90]. Hypoxia, and other growth factors, may contribute to VEGF expression within the tumor [91], which induces angiogenesis from existing vasculature and results in the formation of numerous small blood vessels that are lined by CD31 and CD34-positive endothelial cells [26,90]. VEGF itself may also participate in monocyte recruitment, as the VEGF receptor 1 (Flt-1) is co-localized with CD68 in GCT and is correlated with in vitro chemotaxis of the monocytes [92]. Assuming only the spindle-like stromal cells metastasize, a blood vasculature origin for the monocytes within the tumor may explain how secondary tumor sites are able to produce osteoclast-like giant cells [1,6,7]. However, stromal cells injected subcutaneously into immunocompromised mice do not produce giant cells [17,28,93]. Moreover, tumor tissues grown on chick