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Systematic Review

Indoleamine 2,3-Dioxygenase: A Novel Immunotherapeutic Target for Osteosarcoma

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Abstract

Introduction: Tumour-emitted molecules induce immunosuppression in the tumour microenvironment. An immunosuppressive enzyme, indoleamine 2,3-dioxygenase (IDO/IDO1), facilitates immune escape in several malignant tumours, including osteosarcoma. Upregulation of IDO establishes a tolerogenic environment in the tumour and the tumour-draining lymph nodes. IDO-induced downregulation of effector T-cells and upregulation of local regulatory T-cells creates immunosuppression and promotes metastasis. **Observations:** Osteosarcoma is the most common bone tumour characterised by immature bone formation by the tumour cells. Almost 20% of osteosarcoma patients present with pulmonary metastasis at the time of diagnosis. The improvement in therapeutic modalities for osteosarcoma has been in a stagnant phase for two decades. Therefore, the development of novel immunotherapeutic targets for osteosarcoma is emergent. High IDO expression is associated with metastasis and poor prognosis in osteosarcoma patients. **Conclusion and Relevance:** At present, only a few studies are available describing IDO's role in osteosarcoma. This review describes the prospects of IDO not only as a prognostic marker but also as an immunotherapeutic target for osteosarcoma.

Keywords: Indoleamine 2,3-dioxygenase, immunosuppression, immunotherapeutic target, osteosarcoma

Introduction

Osteosarcoma is the most common primary malignancy of the bone.[1] It has a high tendency for local invasion and metastasis.[1] Osteosarcoma is highly heterogeneous by nature.[2-5] The genomic processes driving the oncogenesis of osteosarcoma are still unrevealed.[2] The current therapeutic options for osteosarcoma patients are a combined chemotherapy regimen and surgery, but the prognosis of metastatic or recurrent osteosarcoma is still disappointing.[1,6] Developing a novel immune checkpoint target may provide hope for metastatic osteosarcoma patients. The immune system plays a pivotal role in osteosarcoma disease progression.[7] Novel immunotherapeutic approaches have been investigated to improve survival.[7] Understanding the involvement of the immune system in osteosarcoma might help in improving patient outcomes.[7] Hence,

osteosarcoma prognosis may be related to immune system functional status.

Tumour cells can escape the immune attack through several mechanisms.[8-11] One of the immunosuppressive mechanisms is the up-regulation of indoleamine 2,3-dioxygenase (IDO). IDO is an intracellular enzyme that degrades tryptophan into kynurenine.[12] High expression of IDO in the tumour and tumour-draining lymph nodes has been observed in breast cancer, colon cancer, melanoma, ovarian cancer, brain tumours, soft-tissue sarcoma, acute myelogenous leukemia and several other cancers.[13-26] IDO inhibits effector T-cells by depleting the essential amino acid tryptophan and augmenting the production of kynurenine metabolites.[12,27] The IDO enzyme is also involved in the induction of differentiation and maturation of regulatory T-cells.[27] Overexpression of IDO induces tolerance and immunosuppression.[28] In cancer, IDO1 expression has been observed in tumour cells and in the tumour microenvironment, which includes endothelial cells, immune cells, fibroblasts and mesenchymal cells.[29,30] Nevertheless, the pathophysiology of IDO in the tumour microenvironment has been explicated.[30] In this review, we look at the role of IDO in osteosarcoma.

Materials and Methods

Evidence acquisition

The search approach applied the following keywords: IDO and osteosarcoma. Three electronic databases (PubMed/MEDLINE, SCOPUS and GOOGLE SCHOLAR) were searched for articles published between 2002 and 2022. The most relevant and specific articles were extracted from the literature.

IDO in osteosarcoma

It has been established that IDO emerged from cancer and can constrain antitumor immunity. It has been observed that IDO is expressed in solid tumours such as osteosarcoma. The role of IDO in the pathogenesis of osteosarcoma is shown in Table 1.

Liebau *et al*., evaluated the IDO as a new adjuvant therapy for osteosarcoma. Using several cytokines, they investigated the IDO induction in human osteosarcoma cell lines (MNNG/HOS, KHOS-240, HOS and MG-63). Furthermore, they analysed IDO expression in these cell lines in activated lymphocytes in the presence or absence of cytokines. They revealed that the IDO activity in osteosarcoma cell lines (HOS and MG-63) increased in the presence of IL-12 and IL-18, besides the established pathway through IFN-γ. These mechanisms were identified for the first time in human osteosarcoma cell lines.[31]

Urakawa *et al*., investigated the expression of IDO and its involvement in the prognosis of osteosarcoma. They determined for the first time that osteosarcoma patients with high IDO expression had a worse clinical outcome. They performed the immunohistochemical analysis on the human tissue specimens of 47 patients with high-grade osteosarcoma. The majority of the cases expressed IDO. Their findings showed that IDO has the potential to be a prognostic marker and immunotherapeutic target for osteosarcoma.[24]

A remarkable advancement has been observed in the field of immunotherapy. Meanwhile, an interest in immunotherapy for osteosarcoma has developed recently. Clinical trials have been conducted to check the efficacy of PD-1/PD-L1 (programmed cell death 1/programmed death ligand 1) inhibitors for treating sarcomas, but the therapeutic response in advanced osteosarcoma patients was unsatisfactory.[32] Hence, Harrison and Schwartz suggested that a combinational therapeutic regimen involving immune checkpoint inhibitors and conventional cytotoxic agents is required for these patients.[33] A recent study explored the relationships between IDO1 and PD-L1 expression in 56 osteosarcoma patients. They performed the immunohistochemistry on formalin-fixed, paraffin-embedded tumour tissues to analyse the expression of IDO1 and PD-L1 and compared it with clinicopathological characteristics and

Table 1: Review of IDO involvement in osteosarcoma

Year	Investigator	Description
2002	Liebau *et al*.[31]	IL-12 and IL-18 can induce IDO expression besides the known pathway via IFN-γ. These mechanisms have been revealed for the first time in human osteosacoma cell lines
2009	Urakawa *et al*.[24]	IDO mediated immune tolerance has role in the tumorigenesis of osteosarcoma and may impact on clinical outcome
2020	Toda *et al*.[34]	IDO and PD-L1 inhibitors may have clinical implications in osteosarcoma patients with metastatic lesions
2021	Ligon *et al*.[35]	An increased concentration of TILs expressing immune checkpoint and immunoregulatory molecules was observed in PMs compared with primary bone tumours (including PD-1, PD-L1, LAG-3, TIM-3, and IDO1)
2022	Fan *et al*.[36]	IDO inhibitor in combination with gemcitabine brings new hope for the improved treatment of osteosarcoma

IDO1: Indoleamine 2,3-dioxygenase, IL-12: Interleukin-12, IL-18: Interleukin-18, IFN-γ: Interferon gamma, TILs: tumour -infiltrating lymphocytes, PMs: Pulmonary metastases, PD-1: Programmed cell death 1, PD-L1: Programmed death ligand 1, LAG-3: Lymphocyte-activation gene 3, TIM-3: T-cell immunoglobulin and mucin domain-containing protein 3

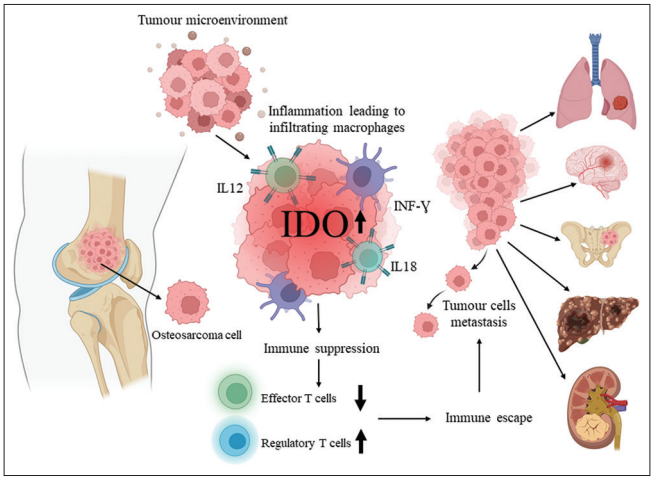

Figure 1: IDO-induced immunosuppression in osteosarcoma. IDO is an immunosuppressive enzyme. IFN-γ is a potent inducer of IDO. IL-12 and IL-18 can also induce the IDO in the tumour microenvironment. IDO inhibits effector T-cell immunity and induces upregulation of regulatory T-cells. High IDO expression is linked with tumour immune escape. IDO-induced immunosuppression might promote metastasis in osteosarcoma patients.

prognosis of the osteosarcoma patients. Moreover, they evaluated the effect of IFN-γ on IDO1 and PD-L1 mRNA expression in human osteosarcoma cell lines (U2OS, SaOS2, MG63 and MNNG). It was observed that IDO and PD-L1 expression was significantly higher in those patients who had already received neoadjuvant chemotherapy than those patients who were treatment naïve. The study concluded that IDO and PD-L1 immune checkpoint inhibitors might be clinically beneficial for osteosarcoma patients with metastasis.[34]

Ligon *et al*., investigated the expression of IDO, PD-1, PD-L1, lymphocyte-activation gene 3 (LAG-3) and T-cell immunoglobulin and mucin domain-containing protein 3 in the tissue specimen of 66 osteosarcoma patients. They revealed that the expression of IDO, PD-1, PD-L1, LAG-3 and TIM-3 was significantly higher in the pulmonary metastases of the patients as compared to the primary tumours. They observed that expression of these molecules in the pulmonary metastases was linked with worse progression-free survival. They demonstrated that

the microenvironment of metastatic osteosarcoma is highly immunosuppressive due to the upregulation of several checkpoint molecules, tumour-associated macrophages and myeloid-derived suppressor cells. They proposed that their findings would provide combinations of agents to develop next-generation clinical trials for osteosarcoma immunotherapy.[35] In a recent study, a group of researchers demonstrated the effect of IDO inhibitor D-1-Methyltryptophan (D-1-MT) in combinational therapy with Gemcitabine (Gem). This gives new hope for the treatment of osteosarcoma patients.[36]

Conclusion

The tumour microenvironment of osteosarcoma is highly immunosuppressive. IDO is well known immunosuppressive enzyme that is upregulated in several cancers, including osteosarcoma [Figure 1].[13-26,24,31] IDO inhibitors as adjuvant therapeutic agents may have clinical implications in osteosarcoma.[36] Since immunosuppression is a hallmark of cancer and a considerable obstacle to cancer immunotherapy. IDO has the potential to be one of the favorable therapeutic candidates for osteosarcoma. Further studies with larger cohorts are warranted to identify the relationship between IDO upregulation and worse prognosis-free survival in metastatic osteosarcoma patients.

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Authors' Contributions

Conceived and designed the analysis: AF and KA; Collected the data: AF, BZ and KA; Contributed data or analysis tools: BZ; Performed the analysis: AF and KA; Wrote the paper: AF, BZ and KA