

Review Article

The Effect of Stem Cells on the Treatment of Undifferentiated Pleomorphic Sarcoma

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Abstract

Stem cells have become therapeutic agents of interest due to their ability to navigate and promote repair in damaged or diseased tissues. Their use has been expanded to modulation of immune response and delivery of targeted treatments such as therapeutic genes or anticancer agents. In the case of cancer, stem cells are being studied both for their antitumorigenic properties and their presence as cancer stem cells within select subtypes. Undifferentiated Pleomorphic Sarcoma (UPS), a subtype regarded as rare among the general population but common among Soft Tissue Sarcoma (STS) patients, shares several of its biological markers and pathways with stem cells, particularly Mesenchymal Stem Cells (MSC). As MSCs have begun to be studied for their anticancer properties and regenerative characteristics post-remission, their application to biologically similar STSs such as UPS remains largely unexplored. The current standard of care for UPS remains one of surgical intervention and toxic chemotherapy drugs, most commonly doxorubicin and ifosfamide. Because of this, stem cell therapies, including use of MSCs, are of interest as an alternative to conventional treatment. Investigation of MSCs as therapeutic targets within UPS is currently being studied, however research on MSCs as therapeutic agents and targeted delivery vectors for the soft tissue sarcoma subtype remain scarce.

Keywords: Stem Cells; Therapy; Undifferentiated Pleomorphic Sarcoma

Abbreviation

ALDH: Aldehyde Dehydrogenase; ASCT: Autologous Stem Cell Transplantation; CSCs: Cancer Stem Cells; CT: Computed Tomography; CDKN2A: Cyclin-Dependent Kinase Inhibitor 2A; CIK: Cytokine Induced Killer Cells; DKK1: Dickkopf WNT Signaling Pathway Inhibitor 1; FGFR2: Fibroblast Growth Factor Receptor 2; FGF23: Fibroblast Growth Factor 23; HDCT: High Dose Chemotherapy; MRI: Magnetic Resonance Imaging; MFH: Malignant Fibrous Histiocytoma; mTOR: Mechanistic Target Of Rapamycin; MSCs: Mesenchymal Stem Cells; OCT4: Octamer-Binding Transcription factor 4; OS: Osteosarcoma; PTEN: Phosphatase and Tensin Homolog; PIK3: Phosphatidylinositol 3-Kinase; pAKT: Phosphorylated protein kinase B; PARP: Poly (ADP-ribose) polymerase; AKT: Protein Kinase B; RB1: Retinoblastoma 1; SP: Side Population; SOX2: SRY-box Transcription Factor 2; P53: Tumor suppressor Protein 53; ULBP: UL-16 Binding Protein; UPS: Undifferentiated Pleomorphic Sarcoma; VGLL3: Vestigial-Like Family Member 3; YAP1: Yes-Associated Protein 1

UPS Origins and Diagnosis

Undifferentiated Pleomorphic Sarcoma (UPS) is a high-grade soft tissue sarcoma previously generalized as Malignant Fibrous Histiocytoma (MFH). While initially believed to originate from histiocytes, studies have recently indicated that UPS tumors likely arise from Mesenchymal Stem Cells (MSCs), leading to their reclassification from MFH to UPS [1]. This rare breed of cancer possesses a lack of cell differentiation, as well as unspecified lineage differentiation and is typically diagnosed on a basis of exclusion after other sarcomas have been ruled out [2].

Lack of identifiable differentiation means that markers signifying specific tissue identity are usually inconsistent and speculative, making it difficult to treat with standard therapies. Distinct sarcoma subtypes, such as leiomyosarcoma or liposarcoma, are ruled out using a combination of histology, immunohistochemistry and more recently molecular testing. Lack of identification aligning with defined entities results in a diagnosis of UPS [2].

In some cases, UPS tumors have stained for general mesenchymal markers such as vimentin, however staining is generally inconsistent and weak for lineage-specific markers (such as desmin and cytokeratin) [3,4]. Tumors may express some resemblance to muscle, nerve or epithelial markers; however, these similarities are often insufficient for reclassification [5]. Early and accurate diagnosis is crucial due to the aggressive and unpredictable nature of UPS, although difficult. MRI and CT scans are used to evaluate the progression of the disease and are used conjointly with tissue biopsy and comprehensive pathological workup for formal diagnosis [6]. While no single genetic marker has been identified, recurring genetic alterations - such as inactivation of tumor suppressor genes like TP53 or RB1 - have been identified as contributing to the pathogenesis of UPS [1].

UPS Characteristics and Presentation

Characteristics and presentation of UPS vary widely due to the diverse compositions it has been found. In patients, UPS typically presents as a painless, enlarging mass in the extremities or trunk and sometimes rarely in the retroperitoneum. Pain or impairment is seen only in advanced cases. MRI and CT scans reveal irregular heterogeneous masses with rapid growth and early metastasis. Light microscopy reveals pleomorphic spindle cells with mitotic characteristics [7,8].

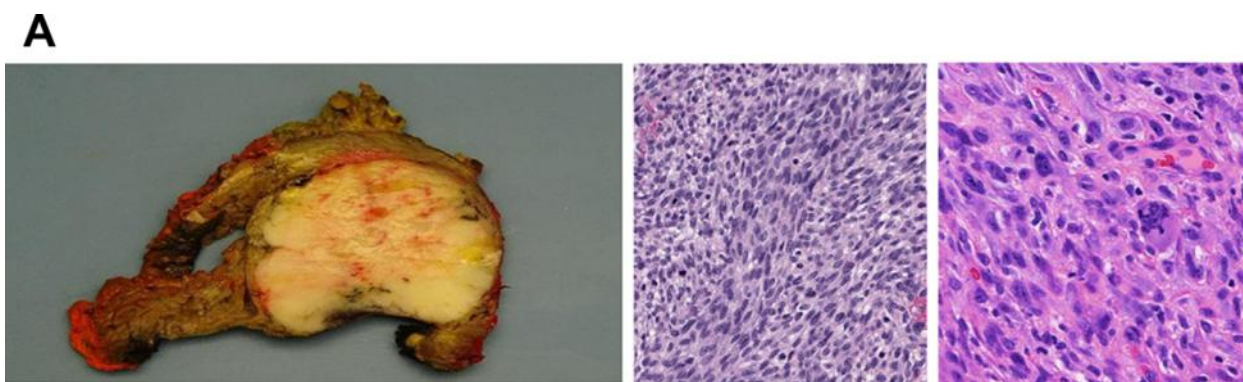


Figure 1: Photo and histology of UPS tumor [2].

Biological Signature and Pathway Dysregulation Profile

While diagnosis of UPS remains one of exclusion, several biomarkers and pathway dysregulations are being studied as potential diagnostic and therapeutic targets. The Side Population (SP) of UPS initiates its tumorigenesis, in which the Hedgehog and Notch signaling pathways appear upregulated [9]. The Hippo pathway appears involved through the presence of VGLL3 and YAP1 in genome sequencing studies [10]. Some studies show documented cases of loss or deletion mutations of PTEN, along with overexpression of pAKT, both involved in the PIK3/PTEN/AKT/mTOR pathway [11-14]. Wnt/B-catenin signaling pathway inhibitor DKK1 also appears to be overexpressed in UPS, more so than in other soft tissue sarcomas. Stem cell gene analysis has also revealed that DKK1 is involved in human MSC differentiation and is likely part of the reason for such similarity in MSC and UPS genetic signatures [25]. Mutations in TP53, CDKN2A, RB1, ATRX, along with gene fusions in TRIO and PRDM10 have also been attributed to UPS [1]. Fibroblast growth factor 23 (FGF23) is also currently being studied as a possible immunohistochemical diagnostic marker for UPS present in bone (UPSb) [16]. Immunohistochemical markers such as vimentin, p53 and Ki67, as well as CD34 and CD68 are expressed in many cases of UPS; however, are typically not used for diagnostic purposes due to their widespread applicability to other diseases [4,17,18].

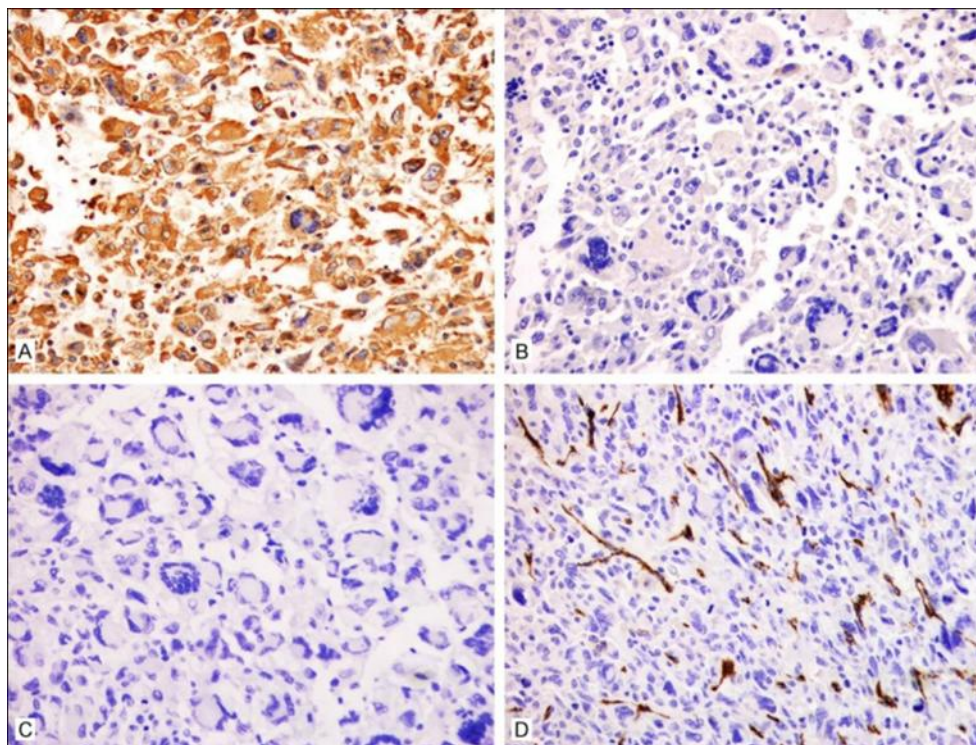


Figure 2. Immunoreactivity of UPS for vimentin (A) and CD34 (D) [4].

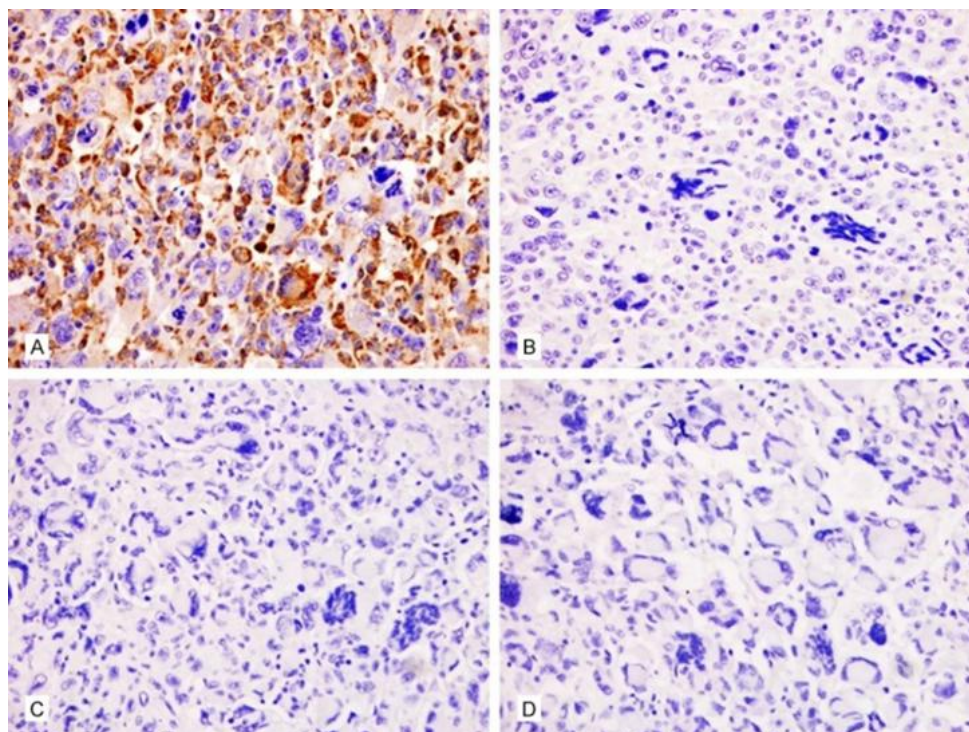


Figure 3. Immunoreactivity of UPS for CD68 (A) [4].

Treatment of UPS

Localized UPS caught in the early stages is typically treated through a surgical approach. Preoperatively, the tumor may be shrunk using radiation therapy to improve surgical outcomes [6]. Surgical intervention includes negative margins to reduce recurrence risk, however this often proves difficult due to proximity to neurovascular bundles. Radiation therapy may also be used postoperatively depending on margins [2,19].

In most cases, chemotherapy is reserved for high-grade or large tumors wider than 5 cm in diameter. Doxorubicin, often with the addition of ifosfamide in conjunction, can be used both neoadjuvantly and adjuvantly in these cases [6,20]. However, the use of doxorubicin is not recommended as a long-term treatment due to its cardiotoxic effects [21]. Gemcitabine is another drug considered in advanced cases and can be used either alone or with docetaxel [22]. This drug combination has been found to be more toxic and difficult to administer, so remains the second line of therapy in metastatic UPS [23]. Gemcitabine has also been considered in combination with dacarbazine and while larger clinical trials are still needed to confirm efficacy, progression-free survival and overall survival rates appear to improve in other soft tissue sarcomas [24]. UPS appears to be one of the few STS subtypes with positive response and prolonged survival when immunotherapy is administered, however further research is needed to analyze its overall efficacy [25].

Discussion

Stem Cell Applications

Previous studies have shown promise for the treatment of cancer with stem cell therapies, especially using MSCs. However, to date, studies regarding stem cells and UPS typically focus on the targeting of subpopulations of Cancer Stem Cells (CSCs) present within the sarcoma subtype, rather than the use of stem cells as therapeutic agents targeting the disease [9,27]. Due to the hypothesized MSC origin of UPS, there exists an overlap in biology that makes it challenging to treat the soft tissue sarcoma with its stem cell predecessor. In several mammalian models, p53 loss in MSC models leads to sarcomagenesis - the process by which sarcoma tumors develop [28]. Not only do MSCs give rise to UPS, but stem-like subpopulations have been found to persist in developed tumors as well [9,27].

MSCs have implications for regenerative medicine due to their ability for self-renewal and differentiation into components such as osteoblasts, chondrocytes and adipocytes [29]. Typically used in musculoskeletal regenerative therapies for orthopedic degenerative diseases, recent studies have begun to consider their application as cancer therapeutics [30,31]. FGFR2, a tyrosine kinase receptor believed to be involved in proliferation of MSCs, has been found to be overexpressed in stem-like UPS subpopulations [32,33]. Dysregulation of FGFR2 has been linked to oncogenic pathways, presenting another complication for the use of MSCs as a therapeutic solution for UPS [33].

CSCs have proven to be a promising target for management of UPS and other soft tissue sarcomas. Cytokine Induced Killer cells (CIK) have been found to target sarcoma CSCs that survive chemotherapy (particularly doxorubicin) and molecular targeted therapy with some success in an *in-vitro* and *in-vivo* mouse model, however clinical significance is still speculative [34].

In Table 1, UPS is shown to express CSC markers such as Oct4, Sox2 and ALDH in varying percentages. Ligands recognized by CIK cells present in UPS populations are also reported in significant amounts, particularly with ULBP 2-5-6 [34].

Trabectedin, an antitumor chemotherapy medication used in the treatment of advanced soft tissue sarcomas, has been found to nearly eliminate CSCs in models where UPS has resulted from transformed MSCs. The use of both trabectedin and camptothecin synergistically boosted apoptotic PARP cleavage and as a pretreatment reduced the ability of UPS cells to form tumor spheres [35].

Pts.	Diagnosis	Age	MICA/B (%)	ULBP1 (%)	ULBP2-5-6 (%)	ULBP3 (%)	CD155 (%)	CD112 (%)	OCT4 (%)	Sox-2 (%)	ALDH high (%)
S1	UPS	67	17	1	99	19	2	1	24	14	3
S3	UPS	86	61	1	100	64	72	3	29	35	4
S5	UPS	72	1	2	97	50	7	2	15	20	8
S16	OS	58	85	7	100	75	20	14	7	44	3
S22	OS	18	49	1	99	60	8	6	10	10	1

Main ligands recognized by CIK (MICA/B, ULBP 1, 3, 2-5-6, CD112 and CD155) were expressed at variable levels by all sarcomas. Average expression of CSC markers Oct4, Sox2 and Aldehyde Dehydrogenase (ALDH) are also reported in the table.

Table 1: Sarcoma cell cultures of patients with UPS and osteosarcoma (OS) [34].

MSCs as a potential cancer therapeutic for UPS poses many obstacles, however there are some avenues that could be pursued to better understand the sarcoma's behavior and reduce cell proliferation. MSC has been found to actively suppress Akt signaling, resulting in anti-tumorigenic activity [36]. The suppression of Akt signaling has been linked to lowered viability and invasiveness of UPS and further research could utilize this pathway along with MSCs to combat UPS [37]. MSCs have also been found to reduce tumor angiogenesis by inducing endothelial cell death and capillary degeneration, suppressing malignancy in *in-vivo* tumor models [38]. While UPS lacks distinct cell types such as endothelial cell populations, further research could investigate potential cytotoxic effects of MSCs on UPS tumors.

The efficacy of hematopoietic stem cells as cancer therapeutics for UPS and other soft tissue sarcomas has remained largely unexplored. A few studies have investigated patient survival with treatment of hematopoietic stem cell transplantation in soft tissue sarcoma after full remission and have concluded that Autologous Stem Cell Transplantation (ASCT) should be further researched in combination with High Dose Chemotherapy (HDCT) to determine improved patient survival rates [39]. The benefit of this approach remains unknown for the UPS subtype.

Conclusion

UPS remains a highly aggressive, variable and mutagenic disease with treatment options largely limited to surgical intervention and toxic chemotherapeutics. Stem cell applications for cancer treatment have shown promise in the past several years, however their application to a UPS model provides many roadblocks. The derivation of UPS from a MSC lineage poses challenges for using stem cells as a therapeutic agent. CSCs present in UPS prove to be targetable subpopulations and show promise as therapeutic targets, however MSCs as a treatment avenue for UPS remains largely unexplored. Biological overlap of MSC and UPS could allow for avenues of biological marker and pathway targeting. Other forms of stem cells, such as hematopoietic stem cells, should be further researched as therapeutic agents due to their lower likelihood of inducing unintentional sarcomagenesis, as seen in MSCs.

Conflict of Interest

The authors declares no conflicts of interest.

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