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Molecular Characterization of Synovial Sarcoma: A Review

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ABSTRACT

Soft tissue sarcomas are tumors that occur in non-epithelial, extraskeletal tissue of the body. Of all the soft tissues sarcomas, synovial sarcoma is one of the most frequently diagnosed and highly malignant. It usually is located distally and within the deep parts of an extremity. The majority of the synovial sarcomas carry t(X;18) (p11.2;q11.2) chromosomal translocation, which makes it a key component in the diagnosis of this malignancy. In this review, we explore the molecular characterizations of this deadly malignancy.

INTRODUCTION

Synovial Sarcoma is a malignancy of the joints that most often occurs in the arm, neck, or leg, with most cases presenting in the lower extremities [1]. Tumor presentation location is near a joint, tendon, or bursa. The tumors consist of cells that contain a chromosomal translocation t(X;18) (p11;q11). This chromosomal abnormality leads to a mutation in the gene, which contributes to the development of synovial sarcoma. It is the fourth most common type of sarcoma and represents roughly 5-10% of all tissue sarcomas in the United States. Synovial Sarcoma most often observed in individuals between the ages of 15-40 years of age, with a higher prevalence found in males than females [2]. There is an estimated incidence of about 900 new cases a year in the United States. Individuals with Li-Fraumeni Syndrome and Neurofibromatosis has shown to be of higher risk. Both are autosomal dominant disorders that lead to a genetic predisposition. Poor prognosis has attributed to distant metastasis, age of older than 25 years, tumor size greater than 5cm, and poorly differentiated areas in histology.

Individuals with synovial sarcoma present with a deep, rapidly growing mass with or without pain. Presenting symptoms are dependent on the location of the tumor: bone metastasis would lead to pathological fracture or lung metastasis leading to pneumothorax or hemoptysis. Imaging, including X-Rays, CT Scans, and MRI Scans, can be used to diagnose sarcoma. Cytogenetic tests looking for DNA errors, as well as an open or core biopsy, the scan, is performed to confirm the presence of synovial sarcoma [3].

For individuals with a tumor size of 5cm or less, surgical resection with or without radiation suggested. Should the tumor size increase 5cm, a multi-disciplinary approach is required utilizing a combination of chemotherapy, radiation therapy, and surgery. As of now, there are no targeted therapies for synovial sarcoma [4]. Though these treatment options may not completely cure synovial sarcoma, the goal is to control the disease while maintaining the best quality of life.

MOLECULAR GENETICS

Synovial sarcoma is one of the rare types of cancer, which only contributes to about 5% of soft tissue sarcoma. It refers to the malignant transformation lading to the cancer formation at the tissues around the joint and the synovium as well [5]. It arises from the synovial membranes around the joint as well as from the synovium itself. Though rare, this type of cancer describes as being very aggressive, and it commonly affects the people within the third and fourth decade in terms of their age. It affects the extremities most widely, with the most frequent sites being the hip, knee, shoulder, and elbow region [5]. However, it can as well change the abdominal walls as the tendons merge. There are two types of synovial sarcoma, monophasic type and the biphasic type [5]. Its clinical presentation in the early stages is very vague and confusing to tell, thus making it be determined when it has advanced. It presents initially as a swollen mass, but later it becomes painful and causes numbness. The pathogenesis behind the development of the synovial sarcoma is due to the genetic mutation affecting various chromosomes. This genetic mutation is thought not to be inherited, but instead, they are acquired mutation, which accumulates overtime to lead to the development of the synovial sarcoma [6]. The modification is perceived to be caused by radiation, certain chemicals that are carcinogenic like arsenic, and long term swelling of the extremities.

S18-SSX fusion

This genetic mutation results from the translocation between chromosome X and chromosome 18. It results in the formation of the fusion gene S18-SSX [7]. The variation found in nearly all the synovial sarcoma, and this though to explain the development [6]. It is through this mutation that synovial cancer develops in the individual. As mentioned before, the genetic variation is thought not to be inherited but rather arises as a result of an acquired mutation. The mutation believed to alter protein synthesis and thus leads to the development of the abnormal proteins. By the formed unusual protein participation in the chromatin remodeling complexes, it spurs oncogenic activity leading to the development of the synovial sarcoma in the affected individuals. The fusion gene, therefore, underlies the mechanism of the development of cancer [8]. It is the hallmark of the synovial sarcoma, and other gene mutation arises following the formation of this fusion gene.

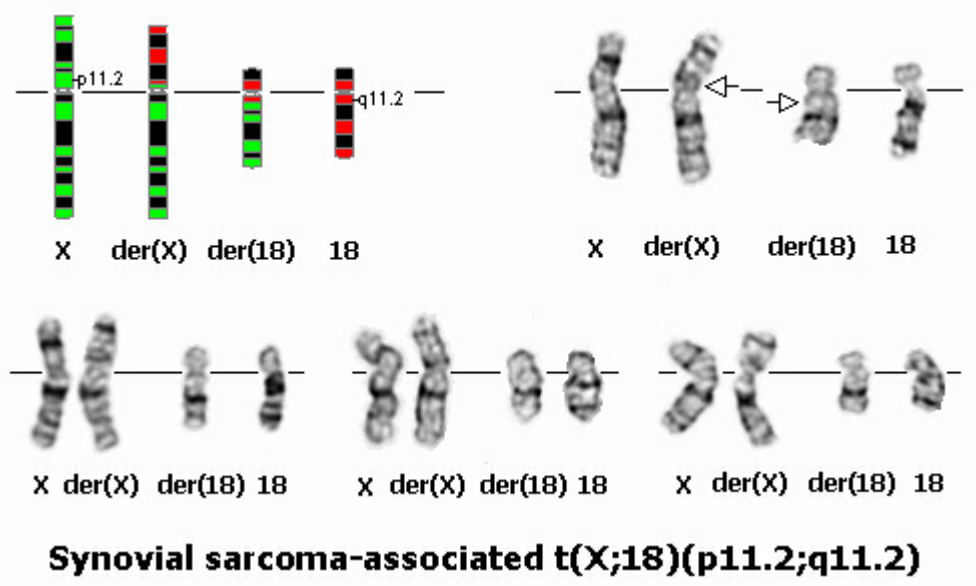

Figure 1:t(X;18)(p11.2;q11.2) in synovial sarcoma G-banding Sarcoma [9]

The mechanism of action of the fusion gene has led to the definition of various therapeutic interventions to halt and reverse the condition among the affected population. In this respect, therefore, a different therapeutic intervention targeting the fusion gene where developed. However, the results have been undesired, and the gene thought to be quite resistant to the interventions targeting the fusion gene as a therapy, which has led to the conclusion that the S18-SSX fusion gene is intractable to the therapeutic measures targeting it as a modality of treatment [5]. Therefore, various other strategies to counter the oncogenic effect of this fusion gene and help manage the condition.

AFFECTED GENE

SS18L1 gene

This gene is located on the short arm of chromosome 20. It is involved in the chromatin remodeling complex through the use of the calcium responsive transactivation. The mutation of the gene is associated with the derangement of the chromatin remodeling complex. This allows for the modification to occur, leading to the development of the malignant cells.

SSX1, SSX2 and SSX4 gene

These genes are located on the long arm of chromosome X and usually translocated with chromosome 18, which function as the transcription protein in the cell. The formation of the fusion is the hallmark of the synovial sarcoma and thus underlies the oncogenic activity of the synovial sarcoma [5]. All three genes form the family of highly homologous synovial sarcoma breakpoint proteins.

SS18 gene

It is located on the short arm of chromosome 18 [8]. In synovial sarcoma, the gene translocates with one of the highly homologous synovial sarcoma breakpoints protein, either of SSX1, SSX2, or SSX4 [10]. This leads to the underlying changes in the development of the neoplasm.

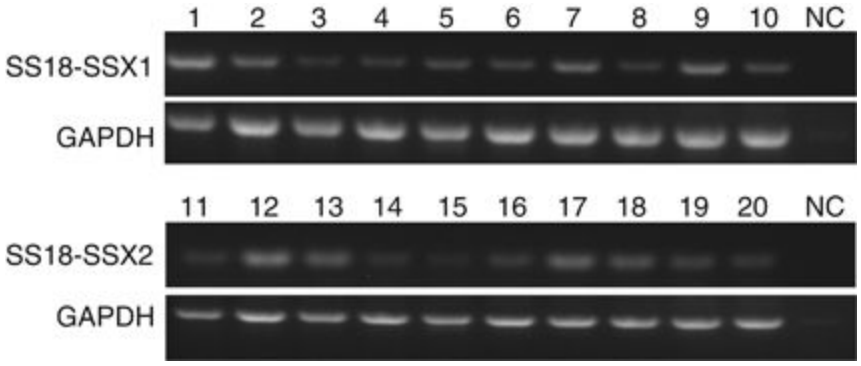

Figure 2: Showing the electrophoresis image of RT-PCR products of the fusion gene [11].

EGFR gene

The epidermal growth factor receptor gene is located on the long arm of chromosome 7. This gene is affected following the development of the fusion gene S18-SSX leading to the deranged functions [10]. The formation of the fusion gene leads to the overexpression of the gene and the resultant protein. The overexpression of the gene and the increase in the sequential protein leads to altered cell proliferation, angiogenesis, and inhibition of the apoptosis, migration, and invasion of the cells, thus leading to the development of the abnormal cells. It contributes to the development of the hallmark of the cancerous cells in which it transforms the healthy cells into abnormal cells. The overexpression of the gene in synovial sarcoma has described in about 63% of patients with the condition [5]. The overexpression of the gene is often affected by other different cancers as well, and thus not specific to the synovial sarcoma.

FGRF2 gene.

The fibroblast growth factor receptor is located on the short arm of chromosome 10. Following the formation of the fusion gene in synovial sarcoma, the gene is as well affected, leading to the upregulation of the receptor on the affected cell of origin. This leads to the promotion of cell growth that bears forth cell proliferation [5]. Therefore, initiation of the therapy hat halts the effects of the fibroblast growth factor receptor leads to impaired cellular growth and proliferation as well as interruption of cellular communication. Advance in the treatment shall as well incorporate using this mechanism in controlling the condition as the research in the management of synovial sarcoma advances.

Apart from the upregulation of the FGFR2 gene and the EGFR gene, the study was done to determine the gene expression related to the S18-SSX fusion gene in synovial sarcoma identified various other affected genes [7]. In the study, the 26 samples from 24 patients with synovial sarcoma were analyzed for the gene expression using the gene expression profiles [10]. The study demonstrated that the S18-SSX fusion gene was associated as well with upregulation of the FOXC1, AGRN, NCAM1, AXL, ZIC2, and SPAG7, among others [5]. This affected gene contributes to the development of the malignant cells among the cell of origin in synovial sarcoma.

Other described mutations in Synovial sarcoma are seen in patients with Li-Fraumeni syndrome and neurofibromatosis 1. They are responsible for the inheritance of the synovial sarcoma among some individuals who harbor these genetic mutations.

METHODS:

The data presented here were gathered via Research Gate, National Center for Biotechnology Information, PubMed, and Google Scholar to identify peer-reviewed articles regarding the molecular characterization of synovial sarcomas.

DISCUSSION: MOLECULAR GENETICS IN THE DIAGNOSIS

TLE1 gene and CD99

Various research has been undertaken to determine whether the TLE1 and CD99 can be used during the immunohistochemistry in the determination of the diagnosis of the synovial sarcoma. According to the acquired results from the 100 cases of the carcinoma stained with TLE1 and CD99, it was evident that none of the synovial sarcomas with SS18 gene stained positive. Other carcinomas, however, stained positive, including adenocarcinoma, among others. Therefore TLE1 and CD99 immunohistochemistry can be successfully used in the evaluation of the synovial carcinoma with SS18 gene mutation [12]. It as well helps to differentiate the synovial sarcoma from the other differential diagnosis. The various studies, including the research done to reevaluate the TLE1 stain for the SS18-SSX fusion gene, have concluded too that there is a positive relationship between TLE1 staining and synovial sarcoma [12].

Molecular genetics in treatment of synovial sarcoma

Since the understanding of the mechanism of the fusion gene S18-SSX, various interventions have been made to help curb the condition among the affected patient [7]. This offers the gene-targeted treatment regimen that is far more superior to the available treatment modalities such as surgery, radiotherapy, and non-specific chemotherapy. Initially, the therapies were tailored to target the fusion gene, but the results were unwelcoming. It led to the disclosure of the fact that the fusion gene is intractable to the regimen targeting it. The treatment options are now expanding, and the development of more regimen is soon being initiated to manage the condition.

The understanding of the mechanism associated with the SS18-SSX fusion gene in treatment has led to the initiation of the regimen that reverses the oncogene expression [7]. Since the fusion gene and associated protein are associated with the BRD9 for functional development, alteration of even a small number of this component is related to the destruction of the sarcomatous cells [13]. The research suggests that BRD9 supports the oncogenic activity of the fusion gene [5]. Therefore targeting to degrade the component is associated with the reversal of the oncogenic activity of the fusion gene. The component is so essential that even a small degradation has a profound effect on damaging the tumor. The treatment approach has, therefore, to focus on utilizing gene manipulation to bring forth the therapeutic effect [5].

MOLECULAR MECHANISM OF ACTION

A malignant neoplasm arising from tenosynovial tissue of the joints and in synovial cells of tendons and bursae. The legs are the most common site, but the tumor can occur in the abdominal wall and other trunk muscles. Synovial sarcoma cells are characterized by a chromosomal translocation taking place between chromosome X and Chromosome 18.An S18-SSX fusion gene resulting from the chromosomal translocation t(X;18)(p11;q11) is characteristic of nearly all synovial sarcomas. This translocation fuses the SS18T (SYT) gene from chromosome 18 to one of three homologous genes at Xp11, SSX1, SSX2, or SSX4.

DNA damage can take many forms, but because their repair is not always precise, double-strand DNA (dsDNA) breaks are among the most dangerous. Indeed, if a DDS break is repaired by nonhomologous end-joining rather than homologous recombination, it can potentially result in the fusion of DNA ends that were not supposed to be joined [14].

Human synovial sarcomas are caused by translocations generating new fusion proteins. Protein fusions resulting from such translocations might lead to cellular deregulation: genes in the vicinity of the recognition sites for the DNA targeting domain could be inappropriately activated (or, alternatively, repressed), resulting in cellular transformation.

In a detailed and compelling study published in this issue of Cell, the mechanism of cellular alteration in human synovial sarcoma is now unveiled

SS18 is an integral subunit of the human SWI/SNF (BAF) chromatin-remodeling complex. It is tightly associated with the catalytic Brg subunit, dissociating from the multisubunit complex at a much higher urea concentration than the well-known BAF47/hSNF5/INI1 or BAF250/ARID1 subunits [17]. Distinct functions for BRM- and BRG-based complexes have been observed in smooth muscle development, osteoblast differentiation,as well as cellular proliferation. Importantly, the SS18-SSX fusion protein becomes incorporated into the BAF complex in place of SS18, and this, in turn, results in the eviction, and subsequently proteasomal degradation, of the BAF47 subunit.

BAF47 is already a well-established tumor suppressor. For example, loss of the BAF47 gene causes extremely aggressive malignant rhabdoid tumors (MRTs), and its re-expression in MRT cells stops their proliferation [16].

It might, therefore, be expected that the eviction of BAF47 also plays a vital role in human synovial sarcoma tumorigenesis. The altered BAF complex binds the Sox2 locus and reverses polycomb-mediated repression, resulting in the activation of this pluripotency gene.

SRY (sex-determining region Y)-box 2, also known as **SOX2**, is a transcription factor that is essential for maintaining self-renewal, or pluripotency, of undifferentiated embryonic stem cells. Sox2 has a critical role in the maintenance of embryonic and neural stem cells. Sox2 is a member of the Sox family of transcription factors, which have been shown to play critical roles in many stages of mammalian development.

Sox2 is uniformly expressed in human synovial sarcoma tumors and is essential for their proliferation, so its anomalous activation may well be transformative.

They are thereby mentioning the evidence of research and clinical findings of two crucial molecular mechanisms involved in the initiation of the disease. The loss of BAF complex, which is a tumor suppressor and the activation of Sox2, which enhances the pathogenesis by the continued proliferation of the pluripotent cells in the body, is seen in the patient suffering from synovial sarcoma.

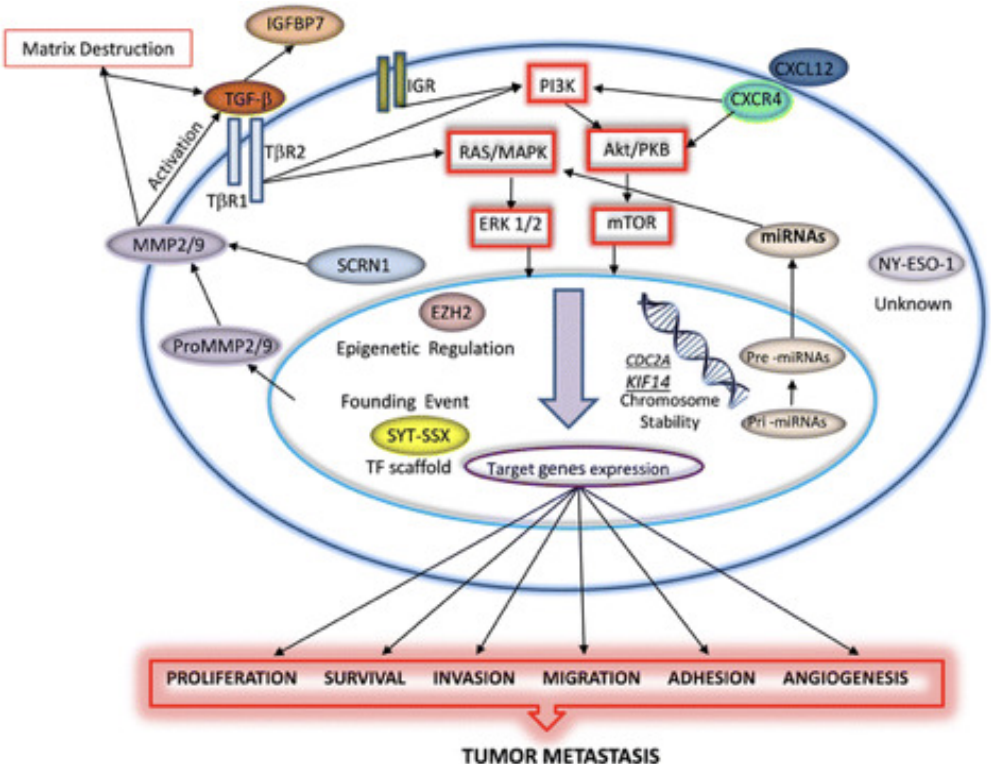

Figure 2: Schematic diagram summarizing the functional relevance of metastatic signals in synovial sarcoma [18]

Schematic diagram summarizing the functional relevance of metastatic signals in synovial sarcoma. SYT-SSX fusion is a founding event in the development of this cancer, which frequently results in the production of molecular signals that promote tumor metastasis. Abbreviations: Akt (Serine/threonine kinase); CDCA2 (Cell division cycle A2); CXCR (Chemokine receptor); ERK1/2 (Extracellular signal-regulated kinase 1/2); EZH2 (Enhancer of zeste homologue 2); IGFBP7 (Insulin-like growth factor-binding protein-7); IGR (Insulin-like growth factor receptor); KIF14 (Kinesin family member 14); MAPK (Mitogen-activated protein kinases); MicroRNAs (miRNAs); MMPs (Matrix metalloproteinases); mTOR (Mammalian Target of rapamycin); NY-ESO-1 (New York esophageal squamous cell carcinoma 1); PI3K (Phosphatidylinositol-3-kinase); pri-miRNA (primary microRNA); pre-miRNA (precursor microRNA); PKB (Protein kinase B); RAS (Ras GTPase); SCRN1 (Secernin-1); TGF-β (Transforming growth factor-beta); TβR (TGF-beta receptor); TF (transcription factor)

Synovial sarcoma is a rare, aggressive subtype of soft tissue sarcoma. It has a predilection for metastases to multiple organs, including the lungs, lymph nodes, and bone. The ability of this tumor to metastasize to multiple organs demonstrates that the tumor can interact and invade multiple environments. The overall prognosis is poor, given the high rate of metastatic disease and the lack of effective therapeutic agents. Nearly all mortality in patients with SS is caused by metastatic disease, yet the biological cause of these events has not been well characterized. The full transformation that occurs with the X;18 chromosomal translocations have not been completely elucidated at this time. Several oncogenic biomarkers have been found to be elevated in SS.

CONCLUSION

As summarized in the diagram above, many of these biomarkers may be used to evaluate for recurrence and metastatic disease and also help determine prognosis. The lack of a full understanding of how the translocation and elevated biomarkers interact with the host is a significant limitation in our ability to treat SS effectively. Further research should be done to help develop a greater understanding of these interactions and the downstream effects that occur in SS, with an emphasis on preventing metastatic disease. This will not only enable patients to be monitored for progression of the disease and allow for counseling regarding prognosis but also be used to develop better treatments for this subtype of soft tissue sarcoma.

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