What relationship exists between leiomyosarcoma, tumor suppressors, and oncogenes?

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Introduction

Understanding the complex interactions between tumor suppressors and oncogenes is crucial for developing effective treatments for leiomyosarcomas, a rare yet aggressive cancer. Leiomyosarcomas account for 10-20% of all soft tissue sarcomas but only 0.1-0.2% of all cancers in the United States (Menon et al., 2024). In addition, research focuses on identifying specific genetic mutations in these genes, intending to develop targeted therapies that are more effective and have fewer side effects than traditional chemotherapy or enhancing chemotherapy's efficacy for leiomyosarcomas. Furthermore, this notion also provides insights into tumor behavior and resistance mechanisms, facilitating a more comprehensive treatment plan for all soft tissue cancers. In light of these advancements, ongoing research, including the use of gene editing technologies such as CRISPR (clustered regularly interspaced short palindromic repeats), is vital for uncovering the underlying mechanisms of leiomyosarcomas. CRISPR potentially offers to correct mutations in tumor suppressors or disable oncogenes, paving the way for highly personalized treatments that improve patient outcomes while minimizing adverse effects (Gupta et al., 2019). Ultimately, such advancements could also lead to preventive strategies for individuals at high genetic risk, significantly transforming the landscape of leiomyosarcoma diagnosis and treatment.

Methods

A literature review has been conducted by searching for existing papers in databases such as PubMed. Boolean operators such as ‘and’ have been used to refine searches and find papers more pertinent to the research. Furthermore, key terms such as ‘RB1 and function’ were used to make the searches. Infographics and additional statistics concerning gene mutations from cBioPortal for Cancer Genomics have been examined and analyzed to conclude the association between leiomyosarcomas, tumor suppressors, and oncogenes. Lastly, the data studied has been plotted using Google Sheets, and these graphs are included in the final paper for readers to reference, enhancing the understanding of the research.

Leiomyosarcomas

Leiomyosarcomas are malignant tumors originating from smooth muscle tissue. These tumors can be found in various parts of the body, including the uterus, gastrointestinal tract, and blood vessels. Additionally, they are notorious for their tendency to metastasize early and quickly, which complicates both treatment and prognosis (Juhasz-Böss et al., 2018).

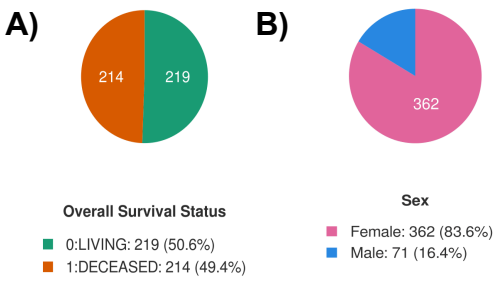


Figure 1. Demographic Data of Leiomyosarcoma Patients. This figure contains data obtained from cBioPortal for Cancer Genomics. Data is presented as two bar graphs. Figure 1A details the survival rate of the patients studied. Figure 1B details the sex of the patients. Number of patients (n) = 433.

The survival rate of leiomyosarcoma patients is approximately 50% (Figure 1A), with a significantly higher proportion of female patients compared to male patients (Figure 1B). Although the exact cause of leiomyosarcoma remains unclear, it is believed to involve complex genetic and molecular mechanisms that transform normal smooth muscle cells into cancerous ones. These tumors present a significant challenge due to their aggressive nature and the difficulty in achieving complete surgical resection, often necessitating a combination of surgery, chemotherapy, and radiation therapy for effective management. Understanding the molecular underpinnings of leiomyosarcomas is crucial for developing targeted therapies to improve patient outcomes. Advances in genomic and molecular profiling technologies have enhanced our knowledge of the underlying biology of leiomyosarcomas, potentially paving the way for personalized treatment approaches. Additionally, investigating novel therapeutic agents, such as targeted therapies and immunotherapies, holds promise for improving outcomes for patients diagnosed with leiomyosarcoma.

Tumor Suppressors -- RB1 and TP53

Tumor suppressor genes, also known as anti-oncogenes, are integral to the body's defense against cancer, as they regulate critical processes like cell growth, DNA repair, and apoptosis (programmed cell death). These genes encode proteins that act as defense mechanisms, ensuring that cells with damaged DNA either repair the damage or undergo apoptosis to prevent potential malignancy. However, when tumor suppressor genes are mutated, this protective mechanism fails, leading to uncontrolled cell growth and, consequently, cancer development, including leiomyosarcoma (American Cancer Society, n.d.). Thus, the study of how these genes become compromised is crucial for identifying therapeutic targets and gaining insights into the pathogenesis of such tumors. Their role in maintaining cellular homeostasis and controlling cell growth underscores their importance as potential targets for interventions aimed at preventing cancer progression. Among these tumor suppressors, the RB1 (retinoblastoma 1) and TP53 (transformation-related protein 53) genes are particularly significant, each playing a distinct but complementary role in safeguarding cellular integrity. RB1 encodes the retinoblastoma protein (pRb), which regulates the transition from the G1 (growth) to the S (synthesis) phase of the cell cycle, thereby preventing uncontrolled proliferation. For instance, mutations in RB1 contribute to the tumor's aggressive behavior (Juhasz-Böss et al., 2018). Conversely, TP53 encodes the p53 protein, which responds to DNA damage by inducing cell cycle arrest or apoptosis, thereby preventing the propagation of potentially tumorigenic cells (Aubrey, Strasser, & Kelly, 2016). In case of a mutation, the cell cycle and apoptosis wouldn’t be regulated, leading to the possible accumulation of mutations. Hence, both genes play a crucial role in maintaining normal cellular function and preventing cancerous growth.

Oncogenes -- CysLTR2

Oncogenes are a type of gene that, when mutated or overexpressed, can transform a normal cell into a cancerous one. These genes exist as proto-oncogenes, which encode proteins that play essential roles in cellular functions such as cell growth, cell division, and apoptosis. Nonetheless, mutations caused by factors such as radiation, chemicals, or viruses can convert proto-oncogenes into oncogenes, leading to abnormal or overactive proteins (American Cancer Society, n.d.). These mutations can occur through point mutations, gene amplifications, chromosomal translocations, or viral introduction, each contributing to the oncogene's heightened activity. Ergo, the study of oncogenes has significantly advanced cancer treatment, allowing for the identification of new oncogenes and the development of therapies tailored to the genetic profiles of tumors. A notable example is the CysLTR2 (cysteinyl leukotriene receptor 2) oncogene, which normally functions in the inflammatory response but can become overactive or mutated in cancers including leiomyosarcoma. In such cases, CysLTR2 drives tumor growth and spread by activating various signaling pathways (Nell et al., 2021). This activation leads to increased cell proliferation, migration, and survival, promoting the aggressive behavior of cancer cells and keeping inflammatory pathways active, which in turn supports tumor growth and resistance to treatment.

Results

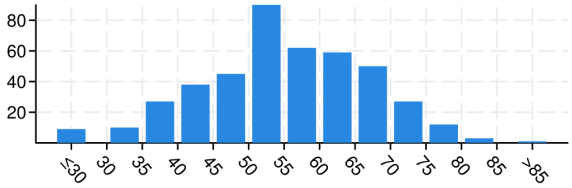


Figure 2. Age Distribution of Leiomyosarcoma Patients. Bar chart displaying the age distribution of individuals diagnosed with leiomyosarcoma, based on a dataset that includes patients aged 21 to 86 years (n=433). The X-axis indicates the age of the patients, and the Y-axis indicates the number of patients. Graph obtained from cBioPortal for Cancer Genomics.

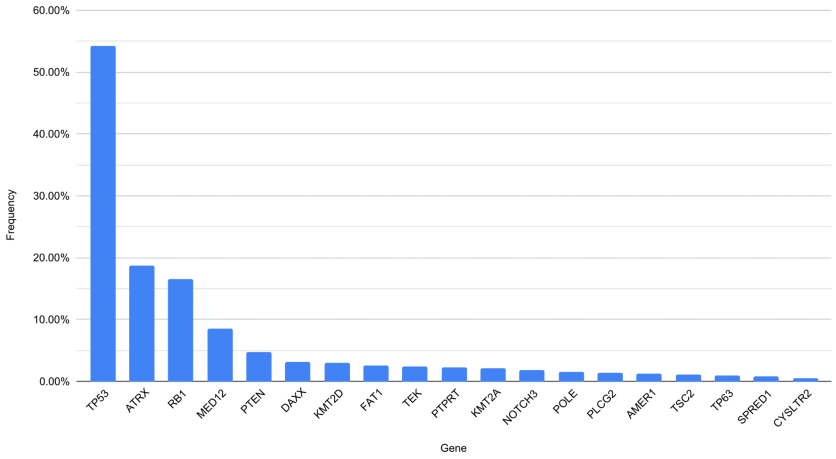
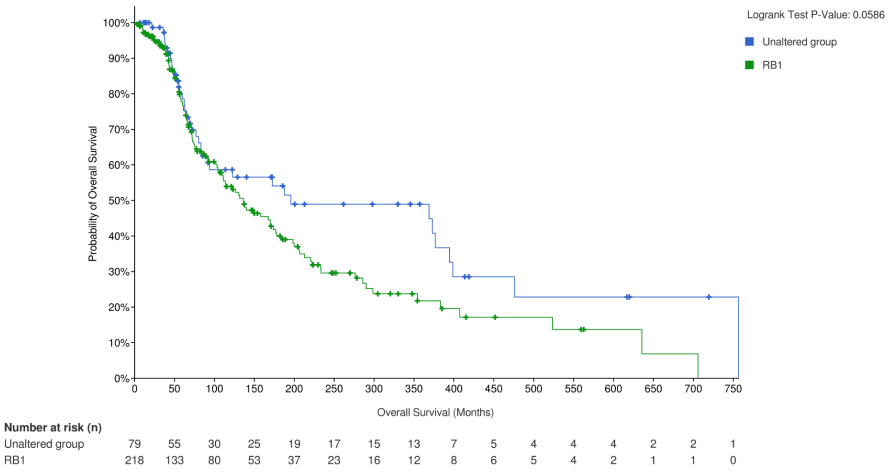


Figure 3. Frequency of Gene Mutations in Leiomyosarcoma. Bar chart illustrates the mutation frequencies of various tumor suppressor genes and oncogenes in leiomyosarcoma samples. Data was obtained from cBioPortal for Cancer Genomics (n = 470). The x-axis

represents specific genes, while the y-axis indicates the percentage of samples in which each gene is mutated.

A)



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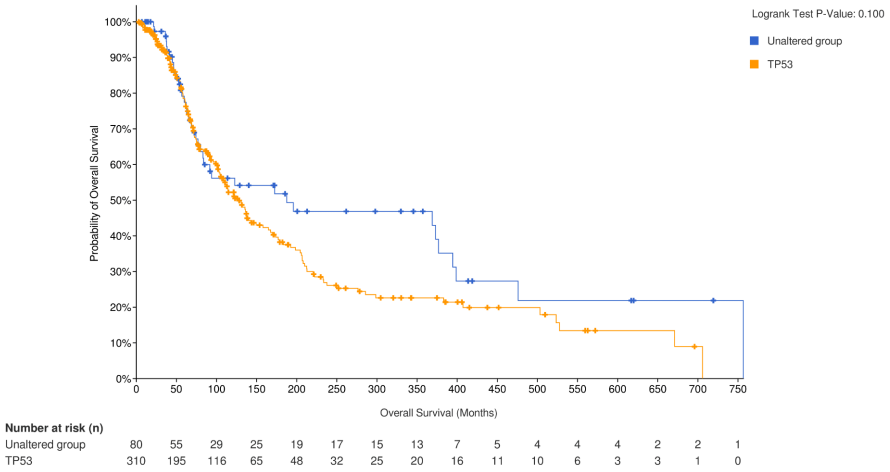

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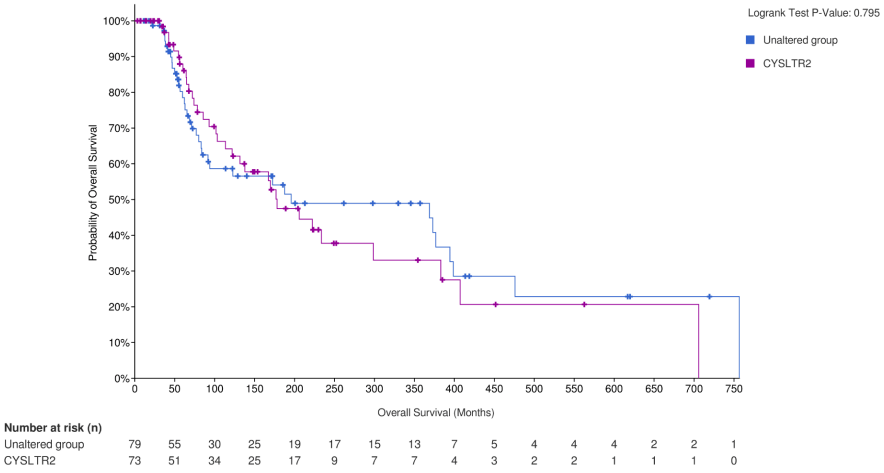

Figure 4. Survival Rate with Altered vs. Unaltered Genes A. Data illustrating the survival rates of patients without RB1 mutations versus patients (n=297) with RB1 mutations. The X-axis represents the number of months survived, and the Y-axis represents the percentage of patients who survived. **B.** Data illustrating the survival rates of patients without TP53 mutations versus patients (n=390) with TP53 mutations. The X-axis represents the number of months survived, and the Y-axis represents the percentage of patients who survived. **C.** Data illustrating the survival rates of patients without CysLTR2 mutations versus patients (n=152) with TP53 mutations. The X-axis represents the number of months survived, and the Y-axis represents the percentage of patients who survived. Graphs obtained from cBioPortal for Cancer Genomics.

By the 50-month mark, both altered and unaltered RB1 patient groups exhibited a decline in survival rates to about 80.5%. Subsequently, by 250 months, survival drops to approximately 50% for unaltered patients, while the altered group sees a sharper decline to around 40%. This gradual reduction highlights the increasing mortality risk over time (Figure 4A). On the contrary, the altered group experiences a different pattern, with a noticeable decrease to 98.12% within just 10 months. From the 100-month mark, their survival rate declines more rapidly, falling below 30% by 250 months and continuing to drop to about 15% by 475 months (Figure 4A). Additionally, the survival trends between the unaltered and TP53-altered groups show significant differences. By 200 months, the unaltered group's survival rate declines to roughly 47%, while the TP53-altered group drops to 40% (Figure 4B). On the other hand, the decline in the TP53-altered group is both more rapid and severe, with survival decreasing to around 47% by 100-150 months and continuing to decline steadily, reaching 0% approximately 50 months earlier than the unaltered group (Figure 4B). In contrast, the survival data for the unaltered and CysLTR2-altered groups reveal different patterns. The unaltered group shows a steady but moderate decline in survival, dropping to about 47% by 200 months, indicating a slow and consistent deterioration over time (Figure 4C). Conversely, the CysLTR2-altered group experiences a less steep decline, with survival decreasing to around 47% by 150-200 months, similar to the unaltered group. Although the decline is less abrupt compared to the TP53-altered group, the survival rate in the CysLTR2-altered group continues to decrease steadily, eventually reaching 0% around 705 months, slightly earlier than the 750 months for the unaltered group (Figure 4C).

Discussion

Survival analysis provides valuable insights into the clinical implications of gene mutations in leiomyosarcoma. Specifically, it examines how mutations in tumor suppressors and oncogenes impact patient survival and disease progression. For the RB1 gene, survival analysis reveals a notable pattern: the altered RB1 group exhibits a faster-declining survival rate compared to the unaltered group (Figure 4A), suggesting that RB1 mutations may have a detrimental effect on long-term survival. RB1 is recognized as a critical tumor suppressor, and its alterations are associated with a worse prognosis in leiomyosarcomas. These findings underscore the necessity of monitoring RB1 status in patients for better prognostic assessments and treatment planning. Similarly, survival data for the TP53 gene highlights its critical role in leiomyosarcomas. The progressive decline in survival rates for patients with TP53 mutations compared to the unaltered group supports the notion that alterations in this gene are linked to adverse outcomes (Figure 4B). TP53, known for its high mutation frequency and role as a tumor

suppressor, significantly influences patient survival and disease progression. The results emphasize the potential benefit of targeting TP53 pathways in developing novel therapeutic strategies for improving patient outcomes. However, the CysLTR2 survival data analysis shows a similar decline in survival rates over time for both altered and unaltered groups (Figure 4C), indicating that CysLTR2 mutations do not correlate with a higher decrease in survival rates. The impact of CysLTR2 mutations appears to be less pronounced in comparison to TP53 and RB1. While CysLTR2's role in prognosis might be less critical, it still contributes to the overall understanding of genetic influences in leiomyosarcomas, helping to identify which genes warrant further study.

Conclusion

In summary, the relationship between leiomyosarcoma, tumor suppressors (RB1, TP53), and oncogenes (CysLTR2) stresses the complex interplay of genetic mutations in influencing patient outcomes. For example, tumor suppressor genes like RB1 and TP53 play pivotal roles in maintaining cellular integrity, and their mutations are strongly associated with poorer survival. Additionally, oncogenes like CysLTR2 also contribute to prognosis but may have a less pronounced impact compared to the major tumor suppressors. Thus, understanding these relationships aids in developing targeted therapies and improving patient management in leiomyosarcomas.

References

Aubrey, B. J., Strasser, A., & Kelly, G. L. (2016). *Tumor-Suppressor Functions of the TP53 Pathway. Cold Spring Harbor perspectives in medicine,* 6(5), a026062. https://doi.org/10.1101/cshperspect.a026062\

Cerami et al. The cBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data. Cancer Discovery. May 2012 2; 401. PubMed.

de Bruijn et al. Analysis and Visualization of Longitudinal Genomic and Clinical Data from the AACR Project GENIE Biopharma Collaborative in cBioPortal. Cancer Res (2023). PubMed.

Gao et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci. Signal. 6, pl1 (2013). PubMed.

Gupta, D., Bhattacharjee, O., Mandal, D., Sen, M. K., Dey, D., Dasgupta, A., Kazi, T. A., Gupta, R., Sinharoy, S., Acharya, K., Chattopadhyay, D., Ravichandiran, V., Roy, S., & Ghosh, D. (2019). *CRISPR-Cas9 system: A new-fangled dawn in gene editing.* Life sciences, 232, 116636. https://doi.org/10.1016/j.lfs.2019.116636

Juhasz-Böss, I., Gabriel, L., Bohle, R. M., Horn, L. C., Solomayer, E. F., & Breitbach, G. P. (2018). Uterine Leiomyosarcoma. *Oncology research and treatment*, *41*(11), 680–686. https://doi.org/10.1159/000494299

Linn, P.; Kohno, S.; Sheng, J.; Kulathunga, N.; Yu, H.; Zhang, Z.; Voon, D.; Watanabe, Y.; Takahashi, C. *Targeting RB1 Loss in Cancers*. Cancers 2021, 13, 3737. https://doi.org/10.3390/canc ers13153737

Menon, G., Mangla, A., & Yadav, U. (2024, February 28). *Leiomyosarcoma.* StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK551667/

Nell, R. J., Menger, N. V., Versluis, M., Luyten, G. P. M., Verdijk, R. M., Madigan, M. C., Jager, M. J., & van der Velden, P. A. (2021). *Involvement of mutant and wild-type CysLTR2 in the development and progression of uveal nevi and melanoma.* BMC cancer, 21(1), 164.

https://doi.org/10.1186/s12885-021-07865-x *Oncogenes, tumor suppressor genes, and DNA repair genes*. American Cancer Society. (n.d.). American Cancer Society, https://www.cancer.org/cancer/understanding-cancer/genes-and-cancer/oncogenes-tumor-suppressor-genes. html