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[A Review of the Heterogeneity of the Subgroups of Atypical Teratoid/Rhabdoid Tumors and its Role in Slowing Therapeutic Advances]

Author: Landon Rogers
Major: Biochemistry and Molecular Biology
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

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One of the most common brain tumors found in infants is the Atypical Teratoid/Rhabdoid Tumor (AT/RT). This tumor is responsible for up to 20% of brain cancer cases in children less than three years old. AT/RT is typically summarized by the loss of part of chromosome 22 resulting in the loss of the SMARCB1/INI-1 gene. The tumor has shown large clinical heterogeneity suggesting possible molecular heterogeneity which has played a large role in slowing therapeutic advances. Recent clinicopathological analysis and bisulfite sequencing studies have found that there are three subgroups of AT/RT that present different clinicopathologic and epigenetic interactions. These studies may give insight into future therapeutic targets and treatment results for patients with AT/RT. Further studies are needed to help identify these subgroup-specific targets before finding potential treatments for this fatal tumor.

Introduction

Atypical Teratoid/Rhabdoid Tumors is a very aggressive brain tumor that is commonly found in infants. These tumors are found in both the infratentorial and supratentorial regions of the brain. AT/RT is responsible for up to 20% of pediatric brain tumors in children under three years old, with 70% of all cases of AT/RT showing up before the age of one year old (2,4). AT/RT is characterized by the loss of or genetic alteration of the long arm of chromosome 22 (4). This results in the loss of or genetic alteration of the SMARCB1/INI-1 gene, which are responsible for the chromatin remodeling SWI/SNF protein complex. This protein complex regulates gene expression and stem cell pluripotency maintenance (3).

Since its recognition in the early 1990's, AT/RT has seen difficulty in diagnosing and

treating the disease. This difficulty in treatment is worrying as the tumor is very fatal, with an average survival around only 17 months (4). There are a number of factors that contribute to the struggle in identifying and successfully treating the tumor. One of these factors is the extremely young age of the patient population, which gives doctors less time to identify the disease and less options in trying to treat the disease as radiation therapy is not recommended in patients less than three years old. The disease is also sporadic, which gives scientists limited cases to study. However, one of the biggest contributing factors as to why it is so difficult to diagnose and treat AT/RT is its clinical heterogeneity. A vast range of results has been seen in both the diagnosis and treatment of the tumor. There are a number of genetic mutations of the SMARCB1 gene that can result in loss of protein function. It is believed that loss of function of this gene is at fault for causing AT/RT, as this is seen in most cases of the disease, but more research is needed in order to confirm this. There are rare instances where SMARCB1 function is retained, and a loss of the SMARCA4 gene is seen (2). This ultimately gives a similar result, as both genes are essential to the SWI/SNF protein complex. The lack of complete understanding of the cause of AT/RT contributes to the difficulty in efficiently and effectively identifying the disease in patients.

One of the biggest aspects that has held back further advances in understanding AT/RT is the large range of response to varying treatment of the tumor. The use of radiation therapy has seen mixed results in patients, with it showing effectiveness at times. However, the large drawback to this treatment is that radiation at this young age is shown to often cause long-term neurocognitive sequelae (4). However, the treatment results that have really stumped doctors and scientists, are the cases in which long-term survival was achieved without radiation therapy. These results show that treatment without long term severe side effects is possible. Yet, this was one of a large variety of results from different treatment options representing the vast clinical heterogeneity that comes from AT/RT. The results of this clinical heterogeneity suggested that there was an underlying molecular heterogeneity that could be responsible for both the difficulty in diagnosis and the wide range of responses to treatment.

Recent Progress

Recent studies have been done that have significantly improved our understanding of AT/RT and its complicated clinical and molecular heterogeneity. One of these studies, done by Torchia et al., 2015, was a clinicopathological analysis of 259 rhabdoid tumors in order to discover molecular subgroups of AT/RT (1). They hoped that by examining many different cases of these tumors and the different treatments, they would be able to identify and link clinical symptoms to the molecular subgroups. In the study, the authors found that there were two main subgroups of AT/RT in the analysis of all the tumors, but importantly noted that there could be more. The first group was mostly supratentorial and involved in brain and neural development while group two was mostly infratentorial and was found to contribute to mesenchymal differentiation. In addition to these two subgroups, they found that the tumors could be further stratified into different risk categories based on ASCL1 gene immunostaining. The ASCL1 gene was also found to play an important role in both location and better 5-year survival. They found that ASCL1 expression was strongly correlated with tumors that were located in the supratentorial region and had a better 5-year survival (1). This study is incredibly significant because it is the first and largest study to clinicopathologically analyze AT/RT. The results from this study will also significantly improve our effectiveness in both diagnosing and treating the tumor by now allowing us to identify patients who are more likely to have better long term survival without radiation and further stratify overall treatment of AT/RT.

Another one of the most important studies in furthering our understanding of AT/RT was done in 2016 by Johann et al. (2). In the paper discussed previously, it was found that there were at least two subgroups of the tumor that contributed towards the heterogeneity of the disease, but it was also noted that there could be more. To better understand the subgroups of the tumor, a study was done to both genetically and also epigenetically analyze AT/RT. It was found that there are three distinct subgroups of AT/RT. They sequenced the genome using two different types of sequencing, DNA and RNA sequencing as well as bisulfite and H3K27Ac chromatin-immunoprecipitation sequencing. The DNA and RNA sequencing found no consistent alterations of the SMARCB1 gene that would indicate a difference in subgroups. However the newer technique of bisulfite and the H3K27Ac sequencing found that there were clear differences in the three subgroups through methylation levels and regulatory factors which helped lead to the identification of the regulatory networks and potential therapeutic targets of the subgroups (2). The three subgroups identified from the study were named TYR, MYC, and SHH. ATRT-TYR was named after its overexpression of melanosomal markers that encode tyrosinase which was unique feature of its subgroup. It is further characterized by a majority infratentorial location and broad SMARCB1 deletions. ATRT-MYC is named for its overexpression of the oncogene MYC. A majority supratentorial location and more focal SMARCB1 deletions further define it. The final subgroup was named ATRT-SHH, named for its involvement in SHH signaling and through its high expression of MYCN and GLI2. The SHH subgroups were found in both infra- and supratentorial locations and were characterized through focal aberrations of SMARCB1 (2). This study of furthering our understanding and knowledge of discovering and defining the subgroups of AT/RT cannot be understated in its progress as it has contributed several important points towards understanding the disease and why it has such a large clinical and molecular heterogeneity. Firstly, it gave us insight into the fact that AT/RT is not a singular entity, but three molecular subgroups. The study's new approach to sequencing also showed that while the subgroups may be genetically similar, they are very different epigenetically. Finally, the identification of the subgroups regulatory networks and pathways may open the road the new subgroup specific therapeutic targets (2).

Discussion

The recent progress made in identifying and understanding the clinical and molecular components of AT/RT has been crucial in advancing along the path towards the end goal of an effective treatment of the disease. While the disease is rare, which leaves scientists and doctors with limited cases and materials to study, the researchers who have worked on this tumor has still managed to provided incredible insights into why we see such a vast range of results to the different treatment techniques of the disease. The results of the initial studies have been further validated by more recent studies done to show the distinction of genetic, epigenetic, and clinical aspects of the three subgroups (5).

There are several new findings that these recent studies have revealed about AT/RT. Importantly, it was found that through utilizing clinical risk factors of the different molecular subgroups, it can be more easily understood how certain patients will respond to specific treatments and which patients have higher chances of survival. Further the discovery and identification of the three specific subgroups that make up AT/RT have given us a deeper understanding of the disease. By identifying the molecular and clinical components of the subgroups, we have learned that AT/RT is not singular, and that treatment and more specific therapeutic targets of the disease may lie within the specific subgroups and their individual regulatory networks as opposed to looking at the tumor as a single unit. More so, epigenetic

characteristics of the subgroups may give more insight into the cellular origins of AT/RT (2).

Since its recognition as its own individual disease, effective treatments of this fatal tumor have been low. This struggle has been further propagated due to inconsistent results in all forms of treatment techniques that have been used. There is a large clinical heterogeneity for AT/RT that has made it very difficult to initially identify, treat, and understand. Despite this, researchers have worked hard to better understand why there is such large variation in all aspects of the tumor. They have been correct in identifying that the clinical heterogeneity results from a molecular heterogeneity that ultimately stems from the tumor being comprised of the three subgroups that have been discussed. Even further, the subgroups have their own amount of heterogeneity to them in several different aspects, that while the discovery of will help identify and improve treatment, have also revealed that treatment for this disease will be complicated. By understanding the difference among the subgroups, it seems likely that the treatment of each subgroup will have to vary. This means that complete effective treatment of AT/RT will be difficult as the correct treatment for each different subgroup and potential variant of subgroup will likely be different.

Despite all the new discoveries in recent years in reference to AT/RT, there is still a lot of work to be done in regard to furthering the ultimate goal of effective treatment. While we know significantly more about the characteristics of the subgroups of AT/RT, more studies will have to be done on the individual subgroups in order to identify certain targets that could be utilized for treatment. Further clinical trials and studies will need to be conducted in order to better correlate the molecular and clinical heterogeneity. There has been great progress made in understanding AT/RT, but there is still more research needed in order to find effective treatments for the disease.

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