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SETD8 and P53 Correlations in Plasma Cell Myeloma

ABSTRACT

Multiple myeloma is a malignant neoplasm of plasma cells with clinical and genetic heterogeneity. Recent work has shown that molecular subtypes and the 70-gene prognostic risk score (MyPRS) significantly correlate with prognosis in myeloma patients. This study reviews 60 cases of multiple myeloma through biopsy smear samples and analyzes its correlation with SETD8, P53, as well as other chromosomal alterations. It was shown that 93% of cases correlated with SETD8 expression, while the P53 results were insignificant and no correlations were observed. While observing this, it was also seen that alterations in 17p and T53 was consistently expressed in these same cases. Such an association can later be used in the future as a preventative measure to myeloma tumor growth and can serve as a way to decrease one's likelihood of developing the disease as a whole.

INTRODUCTION

About 1 in 143 people develop plasma cell myeloma, which has a survival rate of 50%, clearly showing how myeloma is a cancer that affects thousands of people in the world. The evolution of myeloma starts when plasmablastic, or cancerous cells, form rapidly. These cells contain a large central nucleus with a high nuclear to cytoplasmic ratio, as well as lack a dominate perinuclear

hof. When a plasma cell becomes abnormal, the body creates antibodies to fight it off, causing blood to thicken, which leads to the bone marrow not producing enough healthy plasma cells. Due to this, the human bone, immune system, and kidneys weaken.

In the past, many new myeloma improvements have been made, and have led to significant results. 10 years ago, myeloma was perceived as incurable, due to a survival rate of approximately 25%, and the main form of treatment being total therapy. Now, both Stage I and Stage II of myeloma are curable diseases, with many cancer institutions straying away from total therapy in favor of immunotherapy: since it is much less taxing on the body. However, with all these new treatments and technology, myeloma patients still have a 1 in 2 chance of not surviving the disease, and still thousands of people are diagnosed with this form of cancer each year. For this reason, it is imperative to have a clear understanding of the cause of development of Plasma Cell myeloma, and how to target or suppress the cause. As seen, in Dr. Shaughnessy's study, myeloma is highly linked with gene expression, and genetics is a major cause as to why some people have myeloma their whole lives, while others never develop it (Shaughnessy et al., 2007).

With this knowledge, it is essential to research the problem and attempt to terminate myeloma, rather than to allow it to form and then treat it. This can be done by finding common genetic trends within myeloma patients. Are there any genes that express in a majority of patients? Do all myeloma patients have the same genetic abnormalities? These are all questions that if answered, can lead to a better understanding of myeloma and a positive future for myeloma patients. If a common gene is found between myeloma patients, researchers can attempt to suppress this gene in people that have it before they develop myeloma, in order to

decrease one's likelihood of being diagnosed with myeloma. Furthermore, this link between specific genetic molecular risk factors can improve the likelihood of a person diagnosed with plasma cell myeloma to be treated with better prognostication, and eventually allow for plasmablastic morphology to be integrated into daily clinical practices. Another study, done by Dr. Huang, shows that microRNA expression is highly linked with genetic factors within myeloma patients, and such genetic factors can affect survival rates in patients (Huang et al., 2012). This clarifies the idea that genetics play a part in all aspects of myeloma; the likelihood of being diagnosed with it, the development of myeloma, the survival rate, and the probability of relapse. As shown by the data, the discovery of a genetic link would not just decrease the number of people diagnosed with myeloma, but also make treatment more precise and effective. Additionally, Dr. Lendavi's publication has shown progress towards finding a link, and even found a possible link of MAGE-C1 and multiple myeloma, however, due to a small sample size his results were ruled insignificant (Lendavi et al., 2009). Although this was the case, Dr. Lendavi's study still makes it known that there is a large possibility to find a direct link with a genetic risk factor and myeloma, and maybe with a larger sample size or database of information, the results may have been deemed significant. This study is still a major marker in myeloma research, and was the first step in understanding and developing more effective treatments for myeloma.

New therapies for myeloma, such as thalidomide and bortezomib, have made the disease much more controllable, and because of this, myeloma patients living 10 to 20 years after being diagnosed has become much more frequent than it was 20 years ago (Mohty et al., 2010). Nonetheless, the average life expectancy after being diagnosed with myeloma is still 4 years,

making it even more crucial to find a link between genetic risk factors and myeloma. This information can help prompt various developments in the future, such as tumor vaccines, which could lead to a decrease in the number of individuals suffering from myeloma; making the average life expectancy statistic less significant. The objective of this study was to identify if and which cytomorphologic features would correlate with genetic molecular risk factors, as well as to gain a better understanding of the causes of myeloma as a whole. Prior to experimentation, it was anticipated that there would be a genetic link, since it is already known that genetics play a major role in many types of cancer, including plasma cell myeloma. Furthermore, a lot of data suggests that genetics is the main factor in the development and progression of multiple myeloma. In the past, the genetic makeup of a myeloma patient has even been used as a way to determine what treatment patients should receive (Feinman et al., 1997). However, this method was not always successful since there was no specific gene that clinicians were looking for. Rather, they looked at the genetic makeup as a whole. With more knowledge of specific genes that cause myeloma, treatments will become significantly more effective and better the lives of many diagnosed patients.

MATERIALS & METHODS

This study consisted of formalin-fixed, paraffin-embedded bone marrow core biopsies from 120 multiple myeloma cases obtained from the clinicians at Mount Sinai Hospital. These bone marrow biopsy samples were all extracted from 2017 to 2019. In addition to such samples, patient demographics, histological features, such as bone marrow core involvement, percent bone marrow aspirate, and plasma cell tumor grades, MyPRS risk score, molecular subtype, and virtually karyotyped gene expression profiles were also recorded and taken into account in this

study. 5 tissue sections from each myeloma patient, originally held in cell blocks, were cut in the Mount Sinai Core Lab and were then stained afterward with SETD8 and TP53. Additionally, thyroid and tonsil samples were also stained to act as a control in the study. The stained slides were digitalized and then electronically analyzed by a computer software and also checked up on and analyzed by researchers every day to look for any changes in the cancer, such as a change in tumor burden, decrease in myeloma stage, et cetera. To ensure statistical significance statistical analysis was performed and verified that the results in the study were not based on coincidence. At the end of the study, the main factors that were considered were the correlation between myeloma morphology and genetics and the relationship between tumor aggressiveness and SETD8 expression.

RESULTS

It was shown that out of the 60 cases reviewed, 53 of them were SETD8 positive, meaning that 93% of the cases showed signs of correlation. Additionally, levels of SETD8 expression differed between the cases. Myeloma samples that had T53 and 17p alterations also had the highest expression of SETD8 - leading to the thought that such alterations may be correlated with myeloma tumor development. The result showed no correlations between P53 and myeloma growth. No alterations consistently were seen in the myeloma cases as well.

DISCUSSION

All in all, it was concluded that while P53 is not correlated with ,myeloma tumor development, SETD8 is. Seeing that 93% of myeloma cases reviewed expressed SETD8 and statistical analysis tests proved the results significant, such a correlation clearly exists. No other

protein showed consistent expression is any of the cases as well, pointing to SETD8 as a lead contributor in myeloma growth. Additionally, histological features did not show any significance within plasma cell myeloma, however some chromosomal alterations did. In particular, the T53 and 17p chromosomes were the two significant alterations with all other possible alterations being ruled insignificant. In the future, there must be research done building off of such findings. I would be interested to work on a genetic suppressor on the SETD8 gene and then see the effects this may have on the further growth of a high risk myeloma tumor.

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