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# The Intersectionality of Muscular Dystrophy and Cancer

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Muscular dystrophy is a group of heritable, neuromuscular disorders that are progressively degenerative to the musculoskeletal system. There are approximately 30 muscular dystrophy disorders, all of which vary according to one's age, the severity of the individual's disorder, and one's affected muscles. Specifically, Duchenne and Becker muscular dystrophies occur due to genetic mutations affecting the production of a complex of proteins called dystrophin. Dystrophin is responsible for strengthening and protecting one's skeletal and cardiac muscles. Without an adequate amount of dystrophin production, atrophy, fibrosis, and muscle degeneration can ensue. While the primary cause of death in this terminal disorder is cardio-respiratory failure, certain cancers have been associated with specific muscular dystrophies. Studies have concluded Duchenne and Becker's are potentially implicative of the development of various types of cancers, such as melanomas, carcinomas, and sarcomas. Similar to that of cancer, muscular dystrophy has no known cure available in modern medicine. Further research on dystrophin's involvement in the onset of cancer is needed and can aid in the understanding of the complexity of muscular dystrophy.

## Introduction

The Duchenne Muscular Dystrophy (DMD) gene is responsible for the production of dystrophin. Dystrophin is a complex of proteins responsible for strengthening and protecting an individual's skeletal and cardiac muscles from impact. Mutations on the DMD gene results in a significant decrease in dystrophin production, thus weakening muscles and potentially leading to atrophy (the degeneration of muscle tissue) and fibrosis (an incurrence of fibrous tissue due to lack of muscular protection from injury) (Singh, 2021).

Approximately 1 in every 5,000-6,000 people assigned the male sex at birth are affected by muscular dystrophy (Romitti et al. 2015). Muscular dystrophy is a group of heritable, musculoskeletal degenerative disorders that currently has no known cure. There are approximately 30 muscular dystrophy disorders, each vary according to one's age, the severity of the individual's disorder, and one's affected muscles. Mutations of the DMD gene are responsible for two specific forms of muscular dystrophies: Duchenne and Becker's.

These dystrophies differ due to Duchenne muscular dystrophy (DMD) causing functioning dystrophin to be completely absent in one's muscles, whereas Becker's Muscular Dystrophy (BMD) causes a small, insufficient amount of functioning dystrophin to be present in one's muscles (Wang et al. 2014). This variation in dystrophin production is ultimately why Becker Muscular Dystrophy is considered to be less severe than DMD, as patients diagnosed with BMD tend to have a higher life expectancy (at least 30 years compared to the 20-year life expectancy in DMD) and less symptoms (Singh, 2021). The smallest isoform dystrophin, Dp71, was found to be maintained in cancer, whilst the largest isoform dystrophin, Dp427, theorized to be a tumor suppressor (genes that encode proteins to constrain cell growth and division), is frequently inactivated in cancer due to a recurrent loss of exons on the 5' end of deoxyribonucleic acid (Wang et al. 2014). Therefore, an inadequate amount of dystrophin, due to the DMD gene, may be associated with cancer.

## Recent Progress

In the Wang et al. (2014) study, intragenic deletions of the DMD gene are frequently utilized by myogenic tumors. Myogenic tumors can lead to the formation of sarcomas that exhibit rhabdomyosarcoma, skeletal muscle differentiation, and leiomyosarcoma, smooth muscle differentiation. Rhabdomyosarcoma is potentially associated with DMD, as evidenced by a few documented cases in males and dystrophin-deficient mice's susceptibility to developing spontaneous

rhabdomyosarcoma (Chandler et al. 2021). It has been proven that dystrophin is expressed in uncontrolled cell proliferation, abnormal tissue growth, rhabdomyosarcoma, leiomyosarcoma, and DMD gene deletions. Dystrophin's involvement in the aforementioned sarcomas confirms dystrophin serves as a tumor suppressor and can inhibit metastases of cancer if regulated. Wang et al. suggests certain therapies recommended for muscular dystrophies, such as corticosteroid medicine, may be applicable to cancer treatment due to dystrophin abnormalities being witnessed in both conditions (2014).

Another similarity between Duchenne and Becker's muscular dystrophies and cancer lies in the musculoskeletal degeneration of both muscular dystrophies and cancer cachexia. Cancer cachexia is resultant in drastic, significant weight loss and muscle degenerative atrophy similar to muscular dystrophy. Cancer cachexia is a syndrome caused by a multitude of factors, such as anorexia, a decrease in physical activity, a decrease in anabolic hormones, and metabolite abnormalities (Berardi 2017). According to Fearon et al. (2011), approximately 80% of cancer patients experience cachexia and cachexia is responsible for 30% of all cancer-related deaths. The syndrome is exacerbated by pro-inflammatory cytokines and inactivation of tumor suppressor proteins (Sukari et al. 2016). Both muscular dystrophies and cancer cachexia exhibit musculoskeletal inflammation, myogenic potential, and dysfunction of the dystrophin protein complex (Berardi 2017). Thus, inferring the potential similar affects both conditions have on the body.

## Discussion

Similar to the findings of Wang et al. and Berardi, Jones et al. (2020) further details the role of DMD gene mutations and dystrophy production irregularities in differing cancer types, such as sarcomas, carcinomas, and lymphoma. The authors highlight certain gaps in research surrounding the intersectionality of DMD gene dystrophies and cancer. Germline mutations to the DMD gene have not been proven to lead to sarcoma predisposition (Jones et al. 2020). There have been readily no studies surrounding the long-term effects of dystrophin decreases in muscular dystrophy patients due to their decreased life expectancy and primary cause of death being cardio-respiratory failure. Approximately 99% DMD gene-related deaths are caused by cardio-respiratory failure (such as cardiomyopathy), pneumonia, multi-organ failure, cachexia, and adrenal insufficiency (Zhang et al. 2017). As treatments discovered in the future begin to decrease the mortality rate of Duchenne and Becker's dystrophes, further research needs to occur surrounding this intersectionality. These future treatments must also consider how their side effects may coincide with tumors.

Future studies are needed to further divulge in the correlation of dystrophin behaving as a tumor suppressor gene and its decrease in presence in both cancer and DMD patients. The frequency of DMD gene mutations, specifically duplications, in both dystrophies and their subsequent alterations of gene expressions also should be evaluated for its potential involvement in disease development via epigenetics (the study of how one's behaviors and environment can result in changes that affect the way one's genes work). Further knowledge of the isoforms Dp427 and Dp71 of the DMD gene alterations should be explored in their involvement in cancer patients. Due to the tumor suppressor nature of both, gene variants should be explored as to whether they serve as oncogenes or tumor suppressors within the body or not. Wang et al (2014) illuminates the necessity for exploring DMD in intra-tumor involvement and the disease's dysregulation in cancer cell functional alterations.

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