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Case Report

ETV-1-Related Cellular Pathways as Targets for Melanoma Chemotherapy

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Abstract

Each anatomical organ in the body possesses a specialized function. Not only are the functionalities different between organs, but their gross appearance is also visibly discernable. On the contrary, at the cellular level, cells from these different organs operate with strikingly similar molecular pathways. We will examine this characteristic in the case of cancerous prostatic cells and melanocytes and its potential to yield novel therapeutic modalities. A literature search was performed to analyze data regarding the intermediates involved in a main cellular pathway observed in both cell types: wnt and β-catenin. Studies on the efficacy of various treatment modalities in prostate cancer were also analyzed. A convincing body of evidence exists, suggesting inhibition of kinases in this pathway leads to inhibition of ETV-1-positive prostate cancer. Certain cases of melanoma were also found to be ETV-1 positive. We hypothesize that MEKi has tremendous potential for exploration as a potential precision therapeutic agent for treatment of ETV-1-positive melanoma. This medical hypothesis stems from the similarities observed in the presence of wnt and β-catenin in both ETV-1-positive prostate cancer as well as melanoma.

Introduction

Although various organs in the human body have different gross anatomies and even perform different functions, at the cellular level, all cells in the body have pathways that share similar intermediates. We will examine this characteristic in the case of neoplastic prostatic cells and melanocytes. Prostate cancer is the second most frequently diagnosed cancer in men and the fifth leading cause of cancer related deaths worldwide, constituting 9% of all cancer deaths [1]. African American men over 60 years of age are at greatest risk and exhibit the highest incidence at 2 times the rate of their Caucasian counterparts [2]. Prostate cancer can be classified into various subtypes that can be identified via genomic analysis [3]. The most common fusion, detected in 45-70% of prostate cancers, is TMPRSS2-ERG [4]. Our previous discovery of the ETS Variant 1 (ETV-1) of the ERG gene has been found to be overexpressed in ~10% of prostate cancers as both a fusion transcript as well as the wild-type form [2-7]. This protein stabilizes β-catenin leading to accumulation and eventual tumorigenesis [2]. Interestingly, it has been shown that ETV-1 and β-catenin are also overexpressed in ~40% and 30% of melanomas respectively [8]. We hypothesize that due to overexpression of both ETV-1 and β-catenin in, ETV-1 may lead to similar downstream effects on β-catenin activity in melanoma as it does in prostate cancer. Demonstrating this relationship in melanomatous cells has the potential to provide new treatment modalities aimed at ETV-1-related pathways. Gaining further insight into the correlation between ETV-1 and the magnitude of clinical presentation in melanoma can pave the way for ETV-1 utilization a diagnostic tool.

β-catenin & ETV-1

β-catenin is involved in cadherin mediated cell-cell adhesion as well as intracellular signaling and transcription modification via the wnt signaling pathway. Studies have demonstrated its ability to regulate embryonic development and tissue maintenance in metazoans [9]. Although β-catenin serves various important purposes, there is also a regulatory mechanism in place to ensure its presence at optimal concentrations. β-catenin is controlled via

ubiquitination and subsequent degradation via phosphorylation, which affects its stability. In the absence of Wnt, β-catenin is phosphorylated via the actions of Gsk-3β, Axin, and APC. In this setting, phosphorylation targets β-catenin for ubiquitination by β-TrCP. In the presence of Wnt, Dsh and GBP inhibit the sequence of β-catenin phosphorylation, ubiquitination, and destruction. As a result, β-catenin continues to accumulate and saturates cytoplasmic β-catenin binding sites. It then translocates to form a complex with the TCF/LEF (T-Cell Factor/Lymphoid Enhancing Factor), a transcription factor (TF) [10].

β-catenin has various functionalities: At the level of the cell membrane, it is a subcomponent of adherens junctions and functions to not only physically reinforce cell-cell contact, but also contributes to contact-inhibition of epithelial cells. In the nucleus, it functions as a transcription factor by co-activating the TCF/LEF TF family, leading to transcription of various genes. It has been clearly demonstrated that mutations in adherens junctions can lead to dysregulation of β-catenin which may then provide a favorable environment for neoplasia. Furthermore, β-catenin has been implicated in a variety of cancers including prostate cancer, melanoma, colon cancer, ovarian cancer, and lung cancer. Çelen et.al. collected over 4,000 cancer-related missense mutations, with gene mapping demonstrating that over 90% of the cancer-related mutations occurred in the exon 3-encoded region of the β-catenin gene [9]. Additionally, both cytoplasmic and nuclear β-catenin are overexpressed in 30% of melanoma cases [11].

ETV-1 is a gene related to the ERG/ETS family members and found to be over-expressed in prostate cancer as a fusion transcript as well as in the wild-type form [2-13]. While full length ETV-1 is expressed in ~10% of patients, the induction of invasion and migration is present in both full-length and truncated ETV-1(dETV1)-expressing prostate cancer cells [14]. dETV1, when transfected into both normal and prostate cancer cells, has been found to increase β-catenin levels through phosphorylation, and render it more stable [2]. However, in the presence of the kinase inhibitor PD98059, these effects can be reversed [2].

Prostatic Adenocarcinoma

The prostate is a walnut-sized gland in the male reproductive system, located posterior to the bladder and anterior to the rectum. The prostate circumferentially surrounds the proximal urethra and functions in producing the seminal fluid and carrying sperm from the testicles upon ejaculation. Adenocarcinoma of the prostate is the second most frequently diagnosed cancer in men and the fifth leading cause of cancer death worldwide, constituting 29% of all cancer cases and 9% of all cancer deaths. African American men exhibit the highest incidence and mortality rate at 2x the risk of developing prostate cancer as compared to their Caucasian counterparts [1,2]. The ERG gene discovered by our lab has been shown to be translocated and expressed at high levels in 45-70% of prostate cancer as the TMPRSS2-ERG fusion transcript [4]. Furthermore, ERG encodes sequence-specific DNA-binding proteins that function as transcriptional activators and lead to carcinogenesis when fused with RNA binding proteins; this is accomplished via inhibiting apoptosis [22].

Melanoma

Melanoma arises from unrepaired DNA damage within melanocytes. These melanin-producing cells are usually found in the stratum basal of the skin's epidermis, the uvea of the eye, and various other anatomical regions. Damage to the melanocytes is most often due to radiation from ultraviolet light and is associated with mutations in the mitogen-activated protein kinase (MAPK) pathway [15]. Melanoma constitutes a mere 5% of skin cancers, however, it causes 75% of deaths from skin-related cancers [16]. The risk factors for melanoma include increasing age, female sex, and Caucasian race. Older age has been associated with an 18% increase in 5-year mortality for patients with stage II disease. For non-Hispanic whites, the most frequently diagnosed age was 70 and over, while 30-39 was most common for Hispanics and Blacks [15]. Women are 30% more likely to have consistent and independent relative advantage in all aspects of localized melanoma as compared to men. For example, women are more likely to have thin lesions that are not ulcerated and located on extremities, as compared to men. The highest incidence, according to the Surveillance, Epidemiology, and End Results (SEER) Program was in Caucasians followed by Hispanics, Asians, and lastly Blacks. However, African Americans tend to present with deeper tumors in a more advanced stage, higher rates of ulceration, and greater metastasis to lymph nodes. As compared to their Caucasian counterparts, African Americans also have a greater cancer-specific mortality for nodular and lentigo melanoma. In addition, low socioeconomic status, which disproportionately affects African American and Latino patients, has been associated with lower 5-year survival rates as compared to those of higher socioeconomic status [9].

Approximately 40% of melanomas have been shown to express ETV-1 amplification. These melanomatous cells are dependent on ETV-1 for growth [17]. In a study by Jané-Valbuena, et al. testing ETV-1 oncogene dependency in melanoma, suppression of EVT-1 triggered a significant decrease in proliferation in 501mel and WW94 cells (cell lines with focal ETV-1 amplification) [18]. In addition, there was a significant decrease in proliferation in the SKMEL28 cell line (without ETV-1 amplification). This suggests that there is ETV-1 dependency in melanoma cell lines with ETV-1 amplification [8]. The ETV-1 gene family has been implicated in the alteration of β- catenin activity by activating kinases that regulate Wnt/β-catenin activity via post-translational modification in prostate cells. Because it has been found that both families are

over-expressed in melanomas, it is plausible to suggest that ETV-1 may have a similar effect on Wnt/β-catenin activity in melanoma cells as it does in prostate cancer cells [2]. This relationship may allow highly targeted treatment modalities of melanoma.

MEK Inhibitors: Therapeutic Potential

Based on the available date, we believe mitogen-activated protein kinase inhibitors (MEKi) are a good candidate for treatment of both prostate cancer and melanoma. MEK pathway inhibitors can overcome the β-catenin phosphorylation pathway and thereby prevent β-catenin accumulation. An example of an MEKi is PD98059; it can reverse the effect of ETV-1 on the Wnt/β-catenin signaling pathway by decreasing both β-catenin accumulation and prostate cancer cell viability. These agents have had a great impact on both prostate cancer prevention and treatment [2]. Tyrosine kinase inhibitors (TKIs) are also incredibly important in the treatment of cancer, due to their frequent relation to mutated oncogenes and tumor suppressor genes. The ability to block various biochemical pathways within the tumor cell via kinase inhibitors has been shown to be an effective method of cancer therapy [19]. The tyrosine kinase inhibitor MP470, when combined with docetaxel has been found to inhibit AXL receptor tyrosine kinase (AXL) as well as block ATP binding cassette B1 (ABCB1), thereby leading to increased apoptosis and decreased migratory and invasive potential in prostate cancer cells; it also leads to decreased docetaxel (a chemotherapeutic agent) resistance in aggressive cancers [20].

TKI-258, a pan receptor tyrosine kinase that targets fibroblast growth receptor, vascular endothelial growth factor receptor, platelet-derived growth factor receptor, fms-like tyrosine kinase 3, and oncogene receptor tyrosine kinase is currently in the clinical trial stage for a variety of cancers (including prostate cancer) as it has displayed anti-tumor activity in pre-clinical trials [21]. Thus, it can be posited that similar treatments can also have a profound therapeutic effect on ETV-1 positive melanoma cells. The first MEK inhibitor approved for melanoma treatment in 2013 is Trametinib (Figure 1). This agent can be used alone or in conjunction with dabrafenib to treat unresectable or metastatic melanoma. Cobimetinib, another MEK inhibitor was approved in 2015 and has the same indications as Trametinib and can also be used alone, or in conjunction with vemurafenib. The most common adverse side effects of these drugs are diarrhea, fatigue, non-acneiform rash, photosensitivity, liver enzyme abnormalities, and elevated CPK levels. Dabrafenib and trametinib are associated with venous thromboembolism, interstitial lung disease, and hypoglycemia and thereby should be avoided in patients with pulmonary diseases or diabetes [20]. In 2011, Reddy et. al. found that histone deacetylase inhibitors such as valproate, an anti-epileptic drug and trichostatin-A can target ERG-positive prostate cancer cells [4-22]. The study found that valproate induced apoptosis in ERG-expressing prostate cancer cells by affecting p53 acetylation as well as inhibit TMPRSS2-ERG expression [22,23]. As similar results were achieved in Ewing family tumors (another cancer found to have ERG family expression), HDAC inhibitors should also be considered for future research on treatment of ETV-1 positive melanoma.

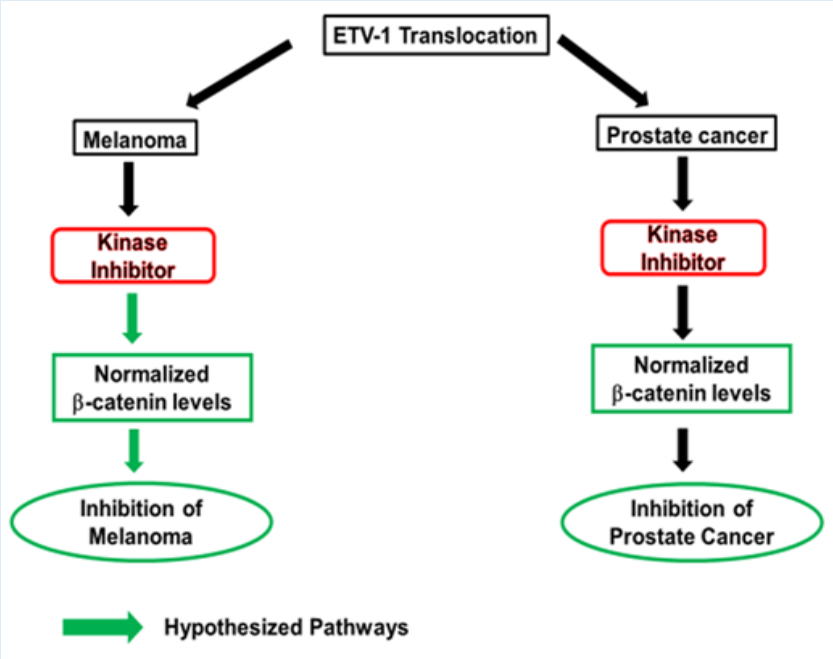

Figure 1: Hypothesized mechanism of β-Catenin regulation in Melanoma. In normal Wnt signaling, β-catenin gets properly phosphorylated and subsequently degraded. β-catenin transfected with dETV1 into cell lines leads to a 2-3-fold increase of β-catenin accumulation. It has been found in studies by Morsalin et.al. that deregulated phosphorylation can cause such abnormal accumulation of inactive β-Catenin in ETV1-positive prostate cancers [2].

Discussion

Precision medicine refers to "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle..." [24]. Currently, medicine is centered around a model of care where treatment and prevention strategies are made for the "average person," which can lead to inaccuracies when determining the best method of treatment for those who are outliers within this model. Precision medicine, unlike personalized medicine is not focused on the individual, but grouped based on a subset of genetic, environmental, and lifestyle factors [24].

Precision medicine, in addition to creating more space for scientists from a variety of specialties to be effective members of the healthcare team, provides a robust understanding of various conditions by way of molecular and genomic information. This, in turn, allows for improvements in choosing medication and predicting their efficacy as well as improvements in preventative care and diagnosis. Our hypothesis examines the molecular aspect of precision medicine. Understanding the molecular similarities in the pathogenesis of prostate cancer and melanoma and how this affects members of varying ethnic groups can allows for the development of novel treatments. While the current mainstay of treatment for prostate cancer is androgen deprivation therapy, patients often progress to advanced castration-resistant prostate cancer [20-23].

Conclusion

The ETV-1 family, which stabilize β-catenin, is over-expressed in both prostate cancer and melanoma. It is postulated that ETV-1 has the same effect on the Wnt/β-catenin pathway in melanoma as it does in prostate cancer. Demonstrating this similarity in mechanisms between the two cell types uncovers new territory for future research by offering highly targeted therapy. In fact, medications such as kinase inhibitors that have been shown to be effective in the treatment of prostate cancer may prove to be efficacious for melanoma treatment [2-21]. In addition, further research on MITF and NRAS cell lines could aid in further understanding of the ETV-1 gene family and thus further treatment options for both prostate cancer and melanoma.

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