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Allergic Rhinitis and Its Impact on Asthma

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Abstract

Phytochromes are dimeric pigment proteins with reversible photochromism between red and far-red light-absorbing forms. They are photoreceptors that regulate various aspects of plant growth and development and have been used for biotechnological applications to improve agricultural performance of crops. *Miscanthus* species have been suggested as one of the most promising energy crops. In this paper, *Arabidopsis* Phytochrome B (PHYB) gene was introduced into *Miscanthus* sinensis using *Agrobacterium* mediated transformation method that we developed recently, with the herbicide resistance gene (BAR) as a selection marker. After putative transgenic plants were selected using the herbicide resistance assay, genomic integration of the transgene was confirmed by genomic PCR and Southern blot analysis, and transgene expression was validated by Northern blot analysis. Compared to nontrans formed control plants, transgenic plants overexpressing PHYB showed phenotypes with increased phytochrome B function, which includes increased chlorophyll content, decreased plant height, and delayed flowering. Therefore, these results suggest that Arabidopsis phytochrome B is functional in *M. sinensis* and provide a method to develop *Miscanthus* varieties with enhanced agricultural performance using phytochromes.

Introduction

Breast cancer refers to cancer proceeding from breast tissue, most commonly from the inner lining of milk ducts or the lobules that grant the ducts with milk. Approximately, breast cancer comprises 10.4% of all cancer cases among women, making it the second most frequent variety of non-skin cancer and the fifth most common cause of cancer death {Cowin, 2005 #35}. It is divided into 4 main subtypes according to its medical molecular characteristics as luminal A and luminal B and HER-2 amplified and triple negative tumors {Panis,2015#49}. Multiple elements contribute to its improvement and progression that's why biology of breast carcinoma is complex {Keen, 2003 #36}. ER negative breast cancer are associated with higher risk of recurrence during first 5 years after treatment as compared to positive ER and risk of cancer is higher in ER positive breast cancer {Ahmad,2013#50}.

Epigenetic regulation has been acknowledged to add three mutually interacting activities – DNA methylation, histone modifications and nucleosome remodeling. These procedures modulate chromatin structure to form euchromatin or heterochromatin, and in turn activate or silence gene expression. {Lo, 2008 #37} Young sufferers under the age of 40 years comprise about 5 to 6 percent of all newly diagnosed instances of breast cancer in the United States yearly. At the time of analysis these patients are usually viewed to have greater aggressive and more advanced tumors {Sariego, 2010 #38}.

There are some techniques used to examine breast cancer these are: Breast Self-Examinations, Clinical Breast Examinations, and Mammography, Full-Field Digital Mammography, Computer-Aided Detection (CAD), Modalities Using Ultrasound, Magnetic Resonance Imaging (MRI), Nuclear Medicine, {Nover, 2009 #39}. The TP53 gene (p53) is found altered in breast carcinomas in approximately 20% to 40% of all instances relying on tumor size and stage of the disease. Chemotherapy is often used to palliate signs in patients with appropriate breast cancer and to limit the risk of recurrence in patients with localized breast cancer. Many chemotherapy drugs have Validated recreation in victims with breast cancer {Foulkes, 2010 #47}. Anthracyclines, such as doxorubicin and epirubicin, are the category of capsules most typically used to treat breast cancer {Hortobagyi, 1998 #43}. It looks to be an early event in breast tumorigenesis. the function of TP53 mutation as a prognostic marker is evaluated as desirable as its role as a predictor for treatment response {Børresen-Dale, 2003 #40}. TNM staging machine is the most ordinary classification developed by means of the American joint Committee on cancer. Another Staging classification Epidemiology, and End Results (SEER) Program {Unger-Saldana, 2014 #41}.

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The prognosis and administration of breast cancer are present procedure a paradigm shift from a one-size-fits-all strategy to the technology of customized medicine. Sophisticated diagnostics, alongside with molecular imaging and genomic expression profiles, enable expanded characterization {McDonald, 2016 #44}.

Triple-negative breast cancer, so referred to as due to fact it lacks expression of the progesterone receptor, estrogen receptor, and HER2, is often, but not now a basal like breast cancer {Foulkes, 2010 #47}. The heterogeneous expression of the Estrogen Receptor (ER), Progesterone Receptor (PR), and HER2 has been noted in different areas of the identical tumors. Moreover discordance, in phrases of ER, PR and HER2 expression, has also been reported between necessary tumors and their matched metastatic lesions {Zardavas, 2015 #45}. More translational lookup is warranted seeing that the World Health Organization (WHO) and International Agency for Research on Cancer (IARC) classify night-shift work as a potential carcinogen. Elucidating how light at night influences breast cancer risk, and whether or no longer melatonin supplementation at night shows any efficacy to give up or deal with breast cancer, should be given pinnacle priority when conducting medical trials to direct future lookup {Grant, 2009 #48}.

Materials and Methods

In this prospective, observational, common clinical practice study, 145 patients receiving prevalent hemodialysis from a single center were tracked for changes in analytical and nutritional parameters from baseline to 12 months (first year of follo prevalent hemodialysis w-up), and mortality was assessed during the second year of follow-up (12 to 24 months). All patients had dialysate calcium concentrations between 1.25 and 1.50 mmol/L. Registration of the causes of death.

Age >18 years and dialysis vintage >6 months were prerequisites for inclusion. Patients were not included if they refused, had HBsAg, anti-HVC, or anti-HIV positive serologies, or had a survival expectancy of less than six months.

Serum iPTH, calcium, phosphorus, alkaline phosphatase, FGF23, 25(OH) vitamin D, C Reactive Protein (CRP), total protein, and albumin were among the analytical parameters. iPTH levels were measured using a second-generation electrochemiluminescence technique in a Roche Elecsys autoanalyzer using antibodies against amino acids 26 to 32 and 55 to 64. This assay recognizes PTH 1-84, long 7-84 fragments, and amino PTH but does not detect short carboxy-terminal fragments [1]. With a limit of detection of 1.2 pg/ml, the intra- and inter-assay coefficients of variation were 2.5% and 3%, respectively. The equation used by the Spanish Society of Nephrology (SEN) to standardize iPTH values [2]. Electrochemiluminescence was used to measure total 25 (OH) vitamin D (D2 and D3) in an Elecsys autoanalyzer (Roche), with limits of detection of 3 ng/ml and intra- and inter-assay coefficients of variation of 7.5% and 8%, respectively. Following the manufacturer's instructions, we measured serum albumin, calcium, creatinine, inorganic phosphorus, total protein, CRP, and alkaline phosphatase using an ADVIA CENTAUR 2,400 autoanalyzer. Two polyclonal antibodies directed to the C-terminus of Fibroblast Growth Factor 23 (FGF-23, C-terminal) were used in an ELISA (Immutopics, USA) to measure plasma levels of FGF-23 (sensitivity: 1.5 RU/ml, intra-assay and inter-assay coefficients of variation: 1.7% and 3.5%, respectively).

Ethics Statement

The Jimenez Díaz Foundation's Institutional Review Board and Ethics Committee gave their approval to the study protocol (Ref. 2016/15). Clinical research adhered to Spanish law and the principles set forth in the Helsinki Declaration. In order to take part in this study, participants must submit written consent.

Statistical Analysis

The median (interquartile range) or mean standard deviation of quantitative data is displayed. The significance threshold was established at p=0.05. Percentages are used to represent qualitative factors. For qualitative data, differences in baseline characteristics were evaluated using the 2 or Fisher's exact test, as applicable, and for quantitative data, the student t test. The Shapiro-Wilk normality test was used to examine the distribution of the data. Wilcoxon signed-rank test was used to examine percent changes from baseline readings. The Mann-Whitney test was used to evaluate the differences between the iPTH readings at baseline and after one year. Spearman correlation was used to assess relationships between various variables. The IBM SPSS Statistics for Windows, Version 20 was used for the analyses (Armonk, NY: IBM Corp).

Results

In the current work a computational effort has been made to improve the thermostability of a haloalkane dehalogenase enzyme, thereby understanding the thermostability mechanism of the enzymes. After a rule based mutant protein design, energy minimization and docking showed all the mutants to be stable not losing their substrate binding affinity with selected ligands. During MD simulation, various properties such as the average values of the Solvent-Accessible Surface Area (SASA) for both hydrophilic and hydrophobic, the Radius of Gyration (RG), the number of inter and intra-protein hydrogen bonds and the number of salt bridges were computed as a function of time.

On the basis of the simulation result, it was observed that the hydrophobic pocket mutant enzyme that contains mutation of amino acids 6ARG/PHE, 7THR/VAL, 35 ARG/PHE, 87 LYS/ILE, 88 SER/VAL, 90 LYS/ILE in the loop region show thermostability. The mechanism of thermostability of hydrophobic mutant was studied that was mainly attributed due to the interaction of 6PHE with 35 PHE and 87 ILE in the surface. Furthermore, at high temperature simulation (at 400 and 500 K), the hydrophobic mutant shows low RMSD confirming the thermostability nature. Surface hydrophobicity is linked to the thermostability in the haloalkane dehalogenase enzyme has been established in this study.

However, this is a computational interpretation, therefore further standardized experimental methods as site directed mutagenesis and enzyme activity analysis is required to establish this concept. The

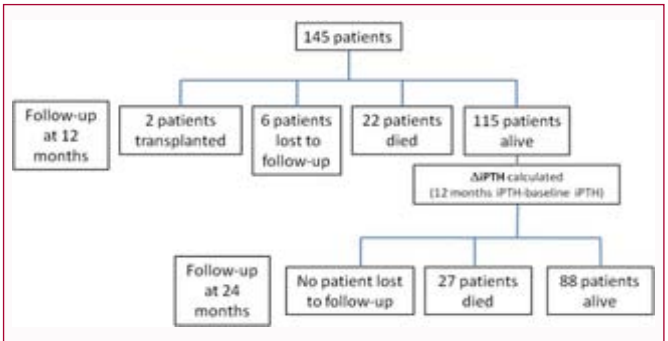

Figure 1: Patient flowchart [3].

whole study offers a general characterization of the computational approaches to design biotechnologically improved thermostable enzymes.

Discussion

The major conclusion of the current study is that, in hemodialysis patients with median baseline iPTH values within the recommended range, iPTH throughout the first year of follow-up is a marker of death during the second year of follow-up. Therefore, even after multivariate correction, a decline in iPTH was linked to increased mortality, whereas a slight increase in iPTH (101 pg/ml to 300 pg/ml) was linked to the lowest mortality.

By using bone histomorphometric standards and the correlation between iPTH levels and overall mortality [3], researchers were able to determine the optimal target iPTH values for hemodialysis [4,5]. However, there is a lot of variation in the reported findings about the correlation between baseline iPTH readings and mortality. The great bulk of research on this association was done using time-fixed survival and baseline iPTH levels. However, iPTH levels are dynamic and alter over time, just like other biological variables. Mortality has been linked to longitudinal variations in serum calcium, phosphate, and calcium x phosphate product [6]. In this regard, only patients who also experienced a contemporaneous decline in Body Mass Index (BMI) over a period of 3 months were found to have an increased risk of all-cause death [7]. The link between iPTH and all-cause mortality was, however, explained by protein energy waste, and iPTH was probably a proxy marker for changes in BMI [7].

Changes in serum iPTH levels were evaluated as categorical factors in a subsequent investigation. The first year of hemodialysis in incident patients was an independent and significant risk factor for cardiovascular death in the following year, but not for all-cause death, heterogeneous definition: 2x lower than the upper limit of normal of the iPTH assay at each center (20). However, the use of a high-calcium dialysate concentration (1.75 mmol/L), which was also independently related with a greater mortality risk [8], was the main cause of the observed drop in serum iPTH. It was not investigated if a reduction in iPTH remaining within the normal-high range was connected with mortality, however patients with low baseline iPTH levels that stayed within the low iPTH range at month 12 did not have an increased risk of cardiovascular death. From the standpoint of the iPTH assay that was used and of dialysate calcium, our study investigated a different research question, the prognostic value of iPTH, independent of baseline iPTH levels or of whether a change in iPTH category occurred, using iPTH as either a continuous variable or a categorical variable in a homogenous population. Furthermore, this was not a problem in our investigation because a high dialysate calcium (1.75 mml/L) was not recommended.

The results of the pan-European COSMOS investigation were consistent with those of the current study [9], despite differences in method and clinical implications. Patients having iPTH levels between 168 and 674 pg/mL at baseline had a decreased mortality, according to COSMOS. Additionally, an increase in iPTH was linked to a lower death rate among patients with low baseline iPTH levels (168 pg/ml), but not in patients with baseline iPTH >168 pg/ml. Our study is the first to demonstrate that a decline in iPTH is related with greater mortality in a hemodialysis cohort with median iPTH values within the guideline suggested range.

In a subsequent investigation, mortality was found to be significantly lower only in patients whose baseline iPTH levels were between 150 and 300 pg/ml [10]. However, there was no difference in the mortality risk between individuals whose blood iPTH levels remained high (>300 pg/mL) and those whose levels dropped from >300 pg/mL to 150 pg/mL to 300 pg/mL.

A J-shaped pattern can be seen in the effect of iPTH during the first year on mortality. Although this association was not significant in patients with greater iPTH levels, a slight increase in iPTH (300 pg/ml) seemed to be linked to a decreased mortality rate. The number of patients with high baseline iPTH levels was too small for any relevant conclusions to be drawn in this regard because this observational trial was conducted as part of usual clinical practice. Possible causes include the use of iPTH-lowering medications, particularly those that have been linked to a reduced chance of survival, as may be the case with high dialysate calcium [11], or nutritional disorders such obesity or malnutrition. However, there was no evidence for these correlations in our population, despite the fact that there were not enough patients to gather substantial data.

Although this observational study cannot prove a cause- and -effect connection, it does offer an intriguing theory with broad therapeutic application: Lowering iPTH may be less safe than allowing it to rise. These findings show that the current method of treating hyperparathyroidism, since a decrease in iPTH is typically the result of a therapeutic intervention. The amplitude of iPTH in response to PTH lowering therapy and mortality have not been well studied in observational research or clinical trials. In randomized trials, prescribing medications that lower serum iPTH did not typically associated with an increase in cardiovascular and all-cause mortality [12,13]. Patients in our study who had a decline in iPTH received any vitamin D treatment more frequently than the other iPTH groups. However, even when iPTH was less than 150 pg/ml, usage of vitamin D receptor agonists was linked to better survival in observational studies [14,15]. In a recent meta-analysis, individuals who were randomly assigned to calcium-based phosphate binders in clinical trials had higher all-cause mortality than those who were assigned calcium-free binders [16]. No changes in phosphate binder type between patients with positive or negative iPTH were found in our investigation.

Since nutritional status affects PTH levels and malnutrition and BMI have been linked to mortality in dialysis patients, nutritional status may be a confounding factor. Low levels of serum albumin have been linked to a reduction in serum iPTH [17], whereas obesity has been linked to greater levels of PTH in the general population [18] and in patients undergoing pre-dialysis [19]. In dialysis patients, PTH is related to BMI and to changes in BMI over time. However, there were no changes between patient groups in the serum albumin levels of the current study.

Our study contains a number of flaws. Cause and effect cannot be investigated because this is observational research. As a single site study with a small sample size, the results cannot be generalized to other centers or nations. The observation of differences that might have been missed in international or multicenter studies, however, may have been aided by the similarity in dialysis initiation and treatment decision criteria.

Finally, dynamic variations in iPTH over time (iPTH) might be more predictive than cross-sectional iPTH levels. The mechanisms behind the observed connection between a decline in iPTH and

mortality when median baseline iPTH levels are within the guideline suggested range need to be further investigated. This knowledge adds to earlier research by providing the unexpected insight that any decline in iPTH is linked to greater mortality. The observation generates a hypothesis, and clinical trials intended to test the theory may change the way that secondary hyperparathyroidism is currently treated in order to improve survival.

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