It is estimated that diabetes affects more than 30 million Americans (CDC, 2015). Prediabetes, a condition in which blood sugar or HbA1c levels are elevated but not to levels permitting a diagnosis of type 2 diabetes, is even more prevalent. Prediabetes precedes the development of type 2 diabetes and for this reason, has been identified as a condition at which interventions might be targeted and progression to overt diabetes might be interrupted. The publication of the initial results of the Diabetes Prevention Program (Knowler WC, 2002) demonstrated that lifestyle change and medication could substantially reduce progression to type 2 diabetes. These efforts have stimulated the CDC to implement the National Diabetes Prevention Program. Unfortunately, a substantial proportion of individuals adhering to lifestyle change or medication still progress to overt diabetes and the identification of individuals participating in a DPP at continued risk for the development of type 2 diabetes would be valuable. We designed a protocol to determine whether individuals responding appropriately to a DPP might be distinguished from individuals at continued risk for diabetes progression by sequential assessments of insulin resistance. We recently validated a multiplexed mass spectrometry assay for the measurement of intact insulin and C-peptide (Taylor SW, 2016), used this to model insulin resistance in individuals undergoing formal assessment of insulin resistance using Steady State Plasma glucose (SSPG) measurements (Abbasi F, 2018) and defined an Insulin Resistance Score (IRS) based on this data. To explore the use of this IRS in the context of an established an IRB approved protocol (Quest Testing to Assess Insulin Resistance [Q-TAIR]; Western IRB protocol # 20171395), we enrolled three cohorts totaling 40 individuals. In addition to anthropometric measurements, this protocol permitted assessment of laboratory data for fasting glucose, HbA1c, electrolytes, lipids, and the IRS at baseline, 1, 3, and 6 months, and 1 year. Data collection is complete for cohorts 1 and 2; data collection is still ongoing for cohort 3. Subjects enrolled in the individual cohorts were enrolled in individual participating practices and varied widely in the proportion offered enrollment based on laboratory test results. In keeping with expectations for adherent participants in a DPP, patients lost an average of 11 lbs. In cohorts 1 and 2, initial IRS were top or middle tertile risk in 10 of 17 patients. Importantly, normalization or improvement of laboratory test results at the conclusion of the DPP did not reflect the continued elevation of IRS risk observed in 5 of the 17 patients. These findings suggest the potential utility of the IRS in assessing changes in the degree of insulin resistance in DPP participants.

Thyroid

THYROID NEOPLASIA AND CANCER

Human Thyroid Cancer Cells Are Highly Sensitive to CDK7 and 9 Inhibition

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Cancer cells display lineage and cancer-specific transcriptional control of expression of oncogenic driver genes, particularly those regulated through super-enhancers. Compounds that target CDK7 and 9, key regulators of RNA polymerase II (RNAPII)-mediated gene transcription, selectively reduce transcription of "superenhanced" oncogenes and are in clinical trials. We previously identified that medullary cancer cell lines are highly sensitive to CDK7 inhibition and that the RET-gene is super-enhanced. In the present study, we sought to determine sensitivities of a panel of follicular cell-derived thyroid cancer cell lines to the CDK7 inhibitor, THZ1 and CDK9 inhibitor, AZD4573. We selected 8 independently confirmed thyroid cancer cell lines (TPC1, FTC133, BCPAP, SW1376; K1, THJ16, C643, and 8505C) from a variety of histological subtypes with different drive mutations and performed WST assays with increasing concentration of THZ1 or AZD4573 to determine IC_{50} for each cell line. Western blots were performed in parallel for target validation. IC_{50} values ranged from 5-100 nM for both compounds for all cell lines. All cell lines showed inhibition of CDK 7 phosphorylation (Ser 5) of RNAPII with retained CDK7 levels with THZ1 and loss of CDK9 RNAPII phosphorylation (Ser 2) with both compounds. However, treatment with either agent unexpectedly caused a reduction of total RNAPII protein levels. qRT-PCR did not reveal reduced mRNA levels in TPC1 cells with THZ1 treatment while, Bortezomib (proteasome inhibitor) co-treatment with THZ1 rescued RNAPII protein. These results are consistent with THZ1-induced proteasome degradation of RNAPII. BRAF protein levels also decreased in the hemizygous BRAF V600E-mutated cell line (8505C) but not the BRAF WT cell line (TPC1). qRT-PCR of both cell lines treated THZ-1 showed stable BRAF gene expression; further mechanistic studies are ongoing. In summary, human thyroid cancer cell lines are sensitive to inhibition of CDK7 and CDK9 likely through several mechanisms not all directly attributable to RNAPII inhibition.