Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS II

MODY3 With Insulin Coding Gene Mutation and Craniofacial Microsomia: A Case Report

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Thyroid

NO LONGER A PAIN IN THE NECK — RECENT INSIGHT INTO THYROID GROWTH, DEVELOPMENT, AND PATHOLOGY

Drug Repurposing Identifies Inhibitors of the Proteostasis Network to Augment Radioiodine Uptake in Combinatorial Approaches Targeting Thyroid Cancer

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New combinatorial drug strategies are urgently needed to improve radioiodide (RAI) uptake and efficiently ablate thyroid cancer cells, thereby reducing the risk of recurrent disease. Drug repurposing offers the promise of identifying already approved compounds capable of inducing sodium iodide symporter (NIS) function to enhance iodide uptake. However, a lack of thyroid cell-based assays amenable to high-throughput screening has limited progress. We utilised the mutated yellow fluorescent protein (YFP) as a surrogate biosensor of intracellular iodide and screened the Prestwick Chemical Library (1200 drugs; 95% approved) for quenching of YFP fluorescence. This allowed us to identify putative candidate drugs which increased iodide uptake >2 SD above mean. Categorisation of these revealed a high proportion of drugs that modulate the proteostasis network (19/48; ~40%), including key processes in protein homeostasis such as endoplasmic reticulum-associated protein degradation (ERAD) and autophagy. Secondary screening validated the activity of proteostasis modulators in enhancing iodide uptake after ranking 73 leading compounds based on their pharmacologic (AUC, Emax and EC50) and specificity of response (NIS+ve vs NIS-ve YFP-thyroid cells) at ten different drug doses (0.1 to 50 μM).

Of importance, several repurposed drugs (e.g. ebastine, Prestwick N, Prestwick C and clotrimazole) in combination with the HDAC inhibitor vorinostat induced a robust enhancement in RAI uptake in thyroid cancer cells (TPC-1 and 8505C NIS+ve cells, up to 11-fold vs DMSO, P<0.001), which was significantly greater than using vorinostat alone (up to 3-fold, P<0.01). For clotrimazole, we designed 7 new chemical derivatives, 3 of which showed enhanced aqueous solubility and retained the ability to significantly enhance RAI uptake. TaqMan RT-PCR revealed that, in contrast to vorinostat, our repurposed drugs failed to alter NIS mRNA expression, highlighting post-transcriptional mechanisms. Critically, 11 repurposed drugs induced significant gains in RAI uptake in human primary thyroid cells (up to 4.1-fold; P<0.05), the most physiological setting for NIS function.

In conclusion, we performed high-throughput screening and identified proteostasis modulators, as well as other repurposed drugs, that markedly enhance radioiodine uptake. Further clinical investigation of these drugs might offer new combinatorial approaches, especially with existing therapies, to improve the treatment of thyroid cancer.