2023 ACG-IRG Pilot Grant

Identifying novel drivers of pancreatic cancer

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Abstract:

While progress has been made in reducing mortality rates for numerous cancer types, pancreatic ductal adenocarcinoma (PDAC) remains exceptionally lethal, exhibiting the lowest 5-year survival rate among major cancers. The fact that few effective treatment options exist for PDAC underscores the urgent necessity for innovative therapeutic approaches. Cancer arises from the concerted action of genetic mutations and epigenetic changes that lead to transcriptional alterations. Although the common genetic mutational landscape of PDAC has been well established, this knowledge has yet to translate into durable treatments. Consequently, attention is shifting towards PDAC drivers that are dysregulated epigenetically rather than through genetic mutations or alterations, making them enticing prospects for therapy. This proposal takes a novel approach to understanding and targeting PDAC, informed by the premise that blocking epigenetically dysregulated pathways that are central to cancer cell growth and survival can reduce tumor growth. Employing an unbiased analysis of super-enhancers (SEs), which are highly active enhancer regions dictating cell identity and behavior by regulating a core set of genes, we have uncovered a wealth of potential PDAC targets that are involved in cancer cell-specific function. Subsequently, we have prioritized these targets functionally through a comprehensive CRISPR/Cas9 knockout dropout screen. Among the top functional candidates, we identified a gene of unknown function: carnitine deficiency-associated gene expressed in ventricle 3 (CDV3). Analysis of publicly available data shows that CDV3 is upregulated in PDAC and that its expression correlates with poor patient survival. Publicly available large-scale analyses reveal that CDV3 binds to RNA and that it interacts with the Myc oncoprotein and the Bmi1 proto-oncoprotein. However, CDV3s function, and especially its potential role in cancer, are completely unknown. We hypothesize that <u>CDV3 plays a pivotal role in driving PDAC and that both CDV3</u> <u>and the pathways it regulates hold promise as potential therapeutic targets</u>. By leveraging cutting-edge RNA and protein interactome technologies and state-of-the-art PDAC models, our proposed studies will provide mechanistic insight into the function of CDV3 in cancer as well as determine the therapeutic potential of modulating its expression. First, we will investigate CDV3's impact on driving proliferation in PDAC cells compared to normal ductal cells. Second, we will uncover CDV3's unique function in cancer by analyzing its RNA and protein interactomes in both cancer and normal cells, as well as elucidating the transcriptional changes induced by loss of CDV3. Finally, we will evaluate CDV3's role in PDAC growth and its effects on chemoresistance through orthotopic transplant models, and its involvement in tumor initiation using a limiting dilution subcutaneous model of PDAC. Our lab's expertise in epigenetics, RNA biology, and pancreatic cancer uniquely poises us to successfully undertake these aims. In summary, this proposal aims to elucidate the function of a potential novel driver of pancreatic cancer, which could provide new avenues for therapeutic intervention that could ultimately improve patient outcomes.