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Mini-Review

Pkhd1l1: A Deafness Gene that Listens to Tumors

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ABSTRACT

The PKHD1L1 (Polycystic Kidney and Hepatic Disease 1-Like 1) protein was initially characterized as an inducible T-lymphocyte receptor but has since proved to have many diverse functions. *Pkhd1l1* regulates hearing and hippocampal neuronal excitability and protects against epileptic seizures. Its expression is associated with better survival rates in older Lung Adenocarcinoma (LUAD) patients. *PKHD1L1* is a potential Tumor-Infiltrating T and B-lymphocyte marker (TIL and TIL-B, respectively). In LUAD, *PKHD1L1* gene is co-expressed with chemokines such as CCL4, CCL5, CCL19, and CXCL9, attracting T-CD8+ cells to the Tumor Microenvironment (TME). In LUAD, *PKHD1L1* transcription primarily correlates with plasma cells, raising the possibility to be involved in Antibody-Dependent Cellular Cytotoxicity (ADCC), Complement-Dependent Cytotoxicity (CDC), and Antibody-Dependent Cellular Phagocytosis (ADCP), suggesting its significance in cancer immunity; therefore, *Pkhd1l1* is a promising target for therapeutic interventions.

Keywords: Deaf; Lung adenocarcinoma; Hearing loss; Phagocytosis

INTRODUCTION

In some cases, it is easy to understand the role of a protein; it helps when the protein has a specific tissue expression and domains with well-characterized functions, however, the Pkhd1l1 protein is not one of them. Initially characterized by Hogan et al., *Pkhd1l1* was shown to be transcribed ubiquitously both in the embryo and the adult mouse [1]. Hogan et al. showed *Pkhd1l1* encodes an inducible T-lymphocyte receptor of unknown function, establishing a link between the *Pkhd1l1* gene and adaptive immunity.

LITERATURE REVIEW

Wu et al. showed the mouse *Pkhd1l1* mRNA is transcribed in the outer hair cells, and the Pkhd1l1 protein is a “stereociliary coat” protein localized on the tips of the stereocilia of the outer hair cells [2]. The *Pkhd1l1* knockouts exhibited progressive hearing loss. Makrogkikas et al. showed that the zebrafish double *pkhd1l1* knockouts; zebrafish have two *pkhd1l1* genes termed *pkhd1l1α* and *pkhd1l1β* also showed hearing deficits [3]. How *Pkhd1l1* regulates hearing is still unknown, although a plausible hypothesis is *via* the interaction of Pkhd1l1 and Anxa4 and Anxa5 [3].

Besides regulating hearing, the mouse *Pkhd1l1* gene maintains neuronal excitability of the hippocampal neurons of the dentate gyrus and protects from epileptic seizures. The dentate gyrus is located in the hippocampus, which is part of the limbic system in the brain. It has a unique, serrated, or "toothed" appearance (hence the name "dentate," which means tooth-like) and is one of the few areas of the brain where neurogenesis occurs throughout life. Yu et al. showed *Pkhd1l1* knockdown in the mouse dentate gyrus overactivates the MAPK/ERK-mCalpain

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pathway, damaging the inhibitory activity of the $GABA_A$ receptor [4].

Like Pkhd1l1, proteins harboring IPT (Ig-like, Plexins, Transcription factors) domains are characterized by a fold similar to that found in Immunoglobulins (Ig) and are involved in various immunological phenomena, such as cell-cell interactions, signaling, and immune responses. Major Histocompatibility Complex (MHC) class I and II molecules, indispensable for the immune response, contain IPT domains and present antigenic peptides to T cells. MHC class I molecules present antigens to $CD8^+$ T cells, while MHC class II molecules present antigens to $CD4^+$ T cells, initiating immune responses against pathogens. T-lymphocyte-Cell Receptors (TCRs), which are essential for the adaptive immune response, also contain IPT domains; they recognize antigens presented by MHC molecules on Antigen-Presenting Cells (APC), leading to T-cell activation. Similarly, to TCRs, B-lymphocyte Cell Receptors (BCR), which mediate antibody immunity, also contain IPT domains. Finally, adhesion molecules like Intracellular Adhesion Molecules (ICAMs) and Vascular Cell Adhesion Molecules (VCAMs), which contain IPT domains, facilitate the interaction between leukocytes and endothelial cells, allowing leukocytes to migrate to sites of infection or inflammation. Indeed, the first characterization of *Pkhd1l1* in the mouse by Hogan et al., highlighted Pkhd1l1 protein as an inducible T-cell receptor for both activated T-$CD8^+$ and T-$CD4^+$ cells, further suggesting a diverse immunological role.

More recently, Kang et al. highlighted the *PKHD1L1* mRNA expression in various types of cancer, including Lung Adenocarcinoma (LUAD) [5]. More specifically, Kang et al. showed a positive correlation of *PKHD1L1* mRNA expression with stages 1-3 of LUAD: From initial tumor formation to localized lung spread, suggesting *PKHD1L1* mRNA is involved in LUAD development or growth. On the contrary, no correlation of *PKHD1L1* mRNA in stage 4 of LUAD was found, suggesting *PKHD1L1* mRNA is not involved in LUAD metastasis. It is possible the absence of correlation between *PKHD1L1* and LUAD stage 4 indicates the substantial heterogeneity present within stage 4 LUAD; therefore, the *PKHD1L1* mRNA might be better suited for detecting disease progression between stages 1-3. In their bioinformatic analysis, Kang et al. revealed *PKHD1L1* mRNA expression was lower in LUAD than in normal tissues. Furthermore, Kang et al. observed that older LUAD patients aged 50 and above, who exhibited higher levels of *PKHD1L1* mRNA, had more favorable survival rates compared to those with lower levels of *PKHD1L1* mRNA expression. Additionally, Kang et al. demonstrated a correlation between tumor-infiltrating activated B- and T-cells (TIL-Bs and TILs, respectively) and *PKHD1L1* mRNA expression.

DISCUSSION

The correlation is significant because TIL and TIL-Bs influence the intricacies of the Tumor Microenvironment (TME) involving tumor-infiltrating immune cells and their role in cancer progression, metastasis, and response to therapy. The TME includes antigens, which influence both the quantity and composition of infiltrating immune cells, thus contributing to a complex immune landscape. In TME, different antigens attract different immune cells, such as T cells, B cells, dendritic cells, and myeloid-derived suppressor cells, which interact with one another and with cancer cells to promote or suppress tumor growth. TME intricacies impact the effectiveness of the immune response against the tumor and highlight the challenge of developing and evaluating new immunotherapies.

In particular, anti-checkpoint therapies, such as PD-1/PD-L1 and CTLA-4 inhibitors, aim to reinvigorate exhausted T-cells to enable T-cells to recognize and kill cancer cells [6].

Diverse and active immune cells within the TME, with anti-tumor phenotypes, associate with a better therapy response. On the contrary, a TME dominated by immunosuppressive cells like regulatory T-cells (Tregs) and Myeloid-Derived Suppressor Cells (MDSCs) can dampen the efficacy of checkpoint blockade.

Kang et al. hypothesize *PKHD1L1* encodes for a TIL-B and TIL marker. Moreover, Kang et al.'s research indicated that, within LUAD, *PKHD1L1* is primarily transcribed in plasma cells (PC). This hypothesis may explain the protective role of *PKHD1L1* against LUAD. High Mutational Burden (HMB) tumors, such as LUAD, tend to generate more neoantigens than low-burden tumors, rendering the tumor recognizable by the immune system and enhancing the immunogenicity of the tumor. HMB tumors present more targets for activated immune cells, leading to a better response to immunotherapy. The *PKHD1L1* gene may play a role in the elevated mutational load of LUAD.

With the advent of spatial proteomics, it is possible to examine if the PKHD1L1 protein is localized on TIL-B and TILs in LUAD biopsies. Spatial proteomic technologies such as the MACSima (Milteniy Biotec) or PhenoImager HT 2.0 (Akoya Biosciences) can accommodate multiple markers. Furthermore, there are established markers for B cells ($CD20^+$), PC ($CD20^-$, $CD79A^+$) and T-CD8 ($CD8^+$, $CD3^+$), and T-CD4 ($CD4^+$, $CD3^+$, $CD8^-$).

The status of *PKHD1L1* as a putative TIL-B and TIL marker prompts further investigation into its role in LUAD survival. Specifically, it necessitates exploring whether *PKHD1L1* functions merely as a bystander gene or if it actively contributes to LUAD patient survival outcomes. Two individual studies, however, argue *PKHD1L1* has a protective role [7,8]. Kang et al. argue that *PKHD1L1* has an active protective role against LUAD: Using bioinformatics, they have shown *PKHD1L1* is co-expressed in LUAD with chemokines such as CCL4, CCL5, CCL19, and CXCL9 that attract T-$CD8^+$ to the TME [5].

Similarly, the status of *PKHD1L1* as a TIL-B marker prompts further investigation and exploration as a contributor to LUAD survival outcomes. PC in the TME contribute to epitope spreading, during which an initial immune response to a neoantigen; not found in normal cells, leads to immune responses to self-epitopes found in normal cells [6]. Epitope spreading thus broadens the immune response against the tumor, potentially increasing the immunotherapy efficacy. *PKHD1L1* may be involved in Antibody-Dependent-Cellular Cytotoxicity (ADCC), during which PC-secreted Antibodies (Ab) decorate the cancer cells, enabling their destruction from Natural Killer (NK)

cells. *PKHD1L1* may also be involved in Complement-Dependent Cytotoxicity (CDC), where antibodies binding cancer antigens activate the complement reaction to attack cancer cells. Finally, *PKHD1L1* may be engaged in Antibody-Dependent-Cellular Phagocytosis, during which PC-secreted Ab decorate the cancer cells and trigger their attack by macrophages.

CONCLUSION

All three putative *PKHD1L1* -associated PC-effector functions can be explored in a *Pkhd1l1* knockout LUAD-Genetically-Engineered-Mouse Model (GEMM). Even though the mouse *Pkhd1l1* knockouts did not reveal overt phenotypes, according to the International Mouse Phenotype Consortium, with the exception of progressive hearing loss as shown by Wu et al., it is possible to detect differences in survival rates between LUAD wt and *Pkhd1l1* knockout mice, that would otherwise remain hidden. Furthermore, should the *Pkhd1l1* knockout LUAD-GEMM proves to corroborate the bioinformatic analysis by Kang et al., it will serve as an excellent testing platform for therapeutic interventions, such as antibodies and chemical inhibitors towards Pkhd1l1 downstream signal-transduction proteins.

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