

## PKHD1L1: A Deafness Gene that Listens to Tumors

Stylianos Makrogkikas<sup>1\*</sup>, Georgios Lolas<sup>2</sup>, Zodwa Dlamini<sup>3</sup>, George Evangelou<sup>4</sup>, Konstantinos N. Syrigos<sup>4</sup>

<sup>1</sup>Department of Chemical Engineering, National Technical University of Athens, Athens, Greece; <sup>2</sup>Department of Integrate Computational and Mathematical Modelling Approaches, National Technical University of Athens, Athens, Greece; <sup>3</sup>Department of Oncology Research, University of Pretoria, Hatfield 0028, Pan African Cancer Research Institute (PACRI), Pretoria, South Africa; <sup>4</sup>Department of Internal Medicine, National and Kapodistrian University of Athens, 11527 Athens, Greece

### 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<sup>+</sup> 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 PKHD1L1 $\alpha$  and PKHD1L1 $\beta$  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 pathway, damaging the inhibitory activity of the GABAA receptor [4].

**Correspondence to:** Stylianos Makrogkikas, Department of Chemical Engineering, National Technical University of Athens, Athens, Greece, E-mail: smakro@chemeng.ntua.gr

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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<sup>+</sup> T cells, while MHC class II molecules present antigens to CD4<sup>+</sup> 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<sup>+</sup> and T-CD4<sup>+</sup> 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.

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 (Miltenyi Biotec) or PhenoImager HT 2.0 (Akoya Biosciences) can accommodate multiple markers. Furthermore, there are established markers for B cells (CD20<sup>+</sup>), PC (CD20<sup>-</sup>, CD79A<sup>+</sup>) and T-CD8 (CD8<sup>+</sup>, CD3<sup>+</sup>), and T-CD4 (CD4<sup>+</sup>, CD3<sup>+</sup>, CD8<sup>-</sup>).

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 [6,7]. 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<sup>+</sup> 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 [8]. 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<sup>-/-</sup> 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<sup>-/-</sup>mice, that would otherwise remain hidden. Furthermore, should the PKHD1L1<sup>-/-</sup>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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