DOI:10.29013/EJHSS-25-3-53-56

THE STRUCTURE OF HUMAN LYMPHATIC VESSEL ENDOTHELIAL HYALURONIC ACID RECEPTOR 1 ASSOCIATED WITH HYALURONIC ACID

Olga Venger [1], ***Denys Oslavskyi*** [2]

[1] Plant Breeding and Genetics Institute – National Center of Seed and Cultivars Investigations, Odesa, Ukraine

[2] Dnipro State Medical University, Dnipro, Ukraine

Cite: *Venger O., Oslavskyi D. (2025). The structure of human lymphatic vessel endothelial hyaluronic acid receptor 1 associated with hyaluronic acid. European Journal of Technical and Natural Sciences 2025, No 3*. https://doi.org/10.29013/EJHSS-25-3-53-56

Abstract

The lymphatic endothelial receptor LYVE-1 plays a crucial role in the uptake of hyaluronan (HA) from the extracellular matrix and facilitates the transit of leukocytes and tumor cells through lymphatic vessels. Furthermore, the conserved oligomeric state of LYVE-1 was confirmed. This study was conducted using bioinformatic approaches, including structural modeling via the SWISS-MODEL platform.

Keywords: *Hyaluronic acid, LYVE-1, lymphatic endothelial cells, SWISS-model service, bioinformatic methods*

Introduction

Human lymphatic vessel endothelial hyaluronic acid receptor 1 (LYVE–1) has been extensively utilized as a marker to distinguish lymphatic endothelial cells (LECs) from blood vascular endothelium (Patnam et. al., 2023). As a receptor for hyaluronic acid, LYVE–1 plays a pivotal role in essential biological processes, including lymphatic trafficking of immune and malignant cells, as well as the development of lymphatic vasculature. Recently, there has been proposed a novel mechanism termed “lymphatic mimicry,” wherein LYVE–1-expressing tumor cells acquire LEC-like characteristics and leverage this receptor to facilitate lymphatic dissemination. Importantly, silencing LYVE–1 expression in tumor cells not only attenuated their lymphangiogenic potential but also significantly reduced metastatic spread in vivo. Furthermore, a recent preclinical study demonstrated that selective depletion of LYVE–1-positive tumor-associated macrophages impairs tumor-associated vasculature and delays disease progression (Lawrance et. al., 2016). These findings underscore the emerging relevance of LYVE–1 as a potential therapeutic and prognostic biomarker in aggressive malignancies, such as breast cancer, where lymph node metastasis (LNM) plays a critical role in determining treatment strategies and patient survival (Nagahara et. al., 2022).

Although numerous studies have examined the association between LYVE–1 expression and clinical outcomes across various cancers, results have been inconsistent. To date, a comprehensive and critical synthesis of the literature evaluating the prognostic utility of LYVE–1 is lacking. Therefore, there has been systematically reviewed and appraised the current evidence to clarify the prognostic significance of LYVE–1 expression in human malignancies and to explore its potential integration into clinical practice (Hu et. al., 2024).

Nevertheless, the structure of LYVE–1 remains still unknown and undiscovered. Therefore, the purpose of the current scientific work was to build and describe the structure of LYVE–1 of human with the help of the SWISS-model.

Materials and Methods

Primary amino acid sequences for which templates were searched and models were built:

MARCFSLVLLLTSIWTTRLLVQGSLRAEELSIQVSCRIMGITLVSKKANQQLNFTEAKEACRLLGLSLAGKDQVETALKASFETCSYGWVGDGFVVISRISPNPKCGKNGVGVLIWKVPVSRQFAAYCYNSSDTWTNSCIPEIITTKDPIFNTQTATQTTEFIVSDSTYSVASPYSTIPAPTTTPPAPASTSIPRRKKLICVTEVFMETSTMSTETEPFVENKAAFKNEAAGFGGVPTALLVLALLFFGAAAGLGFCYVKRYVKAFPFTNKNQQKEMIETKVVKEEKANDSNPNEESKKTDKNPEESKSPSKTTVRCLEAEV.

Template Search

Template search with BLAST and HHblits has been performed according to the SWISS-MODEL template library (SMTL, last update: 2025-03-19, last included PDB release: 2025-03-14) (Bienert, 2017).

The target sequence was searched with BLAST against the primary amino acid sequence contained in the SMTL. A total of 21 templates were found.

An initial HHblits profile has been built using the procedure outlined in, followed by 1 iteration of HHblits against Uniclust30. The obtained profile has then been searched against all profiles of the SMTL. A total of 373 templates were found.

Template Selection

For each identified template, the template's quality has been predicted from features of the target-template alignment. The templates with the highest quality have then been selected for model building.

Model Building

Models are built based on the target-template alignment using ProMod3 (Studer et al., 2020). Coordinates which are conserved between the target and the template are copied from the template to the model. Insertions and deletions are remodelled using a fragment library ProMod3 (Studer et al., 202q). Side chains are then rebuilt (Waterhouse et. al., 2018). Finally, the geometry of the resulting model is regularized by using a force field.

Model Quality Estimation

The global and per-residue model quality has been assessed using the QMEAN scoring function (Studer et al., 2020).

Ligand Modelling

Ligands present in the template structure are transferred by homology to the model when the following criteria are met: (a) The ligands are annotated as biologically relevant in the template library, (b) the ligand is in contact with the model, (c) the ligand is not clashing with the protein, (d) the residues in contact with the ligand are conserved between the target and the template. If any of these four criteria is not satisfied, a certain ligand will not be included in the model. The model summary includes information on why and which ligand has not been included.

Oligomeric State Conservation

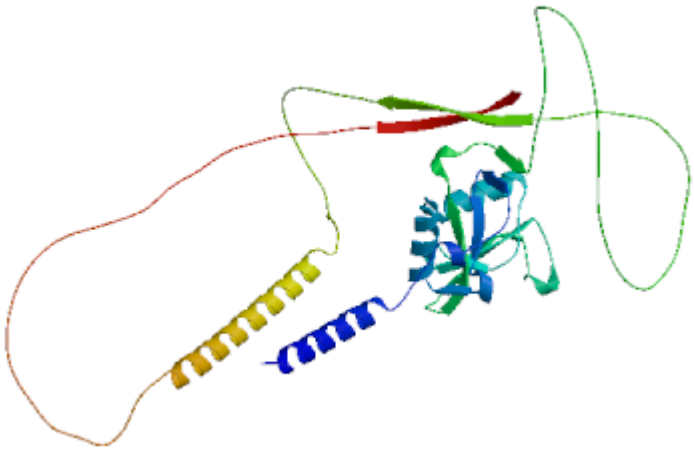
The quaternary structure annotation of the template is used to model the target sequence in its oligomeric form. The method (Bertoni, 2017) is based on a supervised machine learning algorithm, Support Vector Machines (SVM), which combines interface conservation, structural clustering, and other template features to provide a quaternary structure quality estimate (QSQE). The QSQE score is a number between 0 and 1, reflecting the expected accuracy of the interchain contacts for a model built based a given alignment and template. Higher numbers indicate higher reliability. This complements the GMQE score which estimates the accuracy of

the tertiary structure of the resulting model. accuracy of the tertiary structure of the resulting model.

Results

The three-dimensional structure of LYVE–1has been built (Figure 1).

Figure 1. *Three-dimensional structure of LYVE–1*



Discussion

As folding-analoges of LYVE–1 protein there was found CD44 antigen and Tumor necrosis factor-inducible protein TSG-6.

Information about three-dimensional structure and partial analogy can help to understand properties and spatial configuration of LYVE–1.

Conclusion

Accordingly to results of the fulfilled research, the three-dimensional structure of LYVE–1 of human had been constructed. Ligands and domains of LYVE–1 were detected. The concept of its structure may be applied for prediction of the human evolution.

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submitted 15.04.2025;
accepted for publication 29.04.2025;
published 26.06.2025
© Venger O., Oslavskyi D.
Contact: emerald-olga@ukr.net