PRESS RELEASE

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Subject line: Highlighting the molecular mechanism underlying pancreatic cancer development

(Gifu, December 9) Researchers visualized the protein binding site of the (pro)renin receptor known to be involved in pancreatic cancer development using an artificial intelligence-based protein structure prediction program. They predicted the 3D shape of this receptor and revealed the presence of hand-shaped grooves, allowing for the binding of multiple proteins. This study provides the first 3D structural insight into the receptor binding and one-to-many interactions, underpinning the functional versatility of this receptor. These findings will increase our understanding of disease pathogenesis and aid us in exploring novel modalities to treat human diseases, including hypertension and cancer.

Background

The (pro)renin receptor [(P)RR] is a cell membrane-bound protein that was originally identified as a potential regulator of the renin-angiotensin system, which is essential for maintaining blood pressure and body fluid balance. (P)RR contributes to the pathogenesis of various diseases, including hypertension and cancer. When this receptor is aberrantly expressed in normal human pancreatic cell lines, genomic instability (alterations in genes and chromosomes) can occur. Such increased receptor expression contributes to the early carcinogenesis of pancreatic ductal adenocarcinoma (PDAC), the most common pancreatic cancer. Researchers have reported that the antibodies against two (P)RR regions, located in the extracellular domain, could reduce the proliferation of human PDAC cells. Although these regions are likely to participate in cell proliferation pathway, their functional significance remains unclear.

Proteins are chains of amino acids. Each protein adopts a unique 3D shape based on its amino acid sequence (the order of amino acid residues). Functionally essential amino acid residues are evolutionarily conserved and clustered to form functional patches on the protein surface. To date, the 3D structure of the (P)RR extracellular domain has not been experimentally determined. In 2021, significant progress in protein 3D structure prediction was made using AlphaFold2 and RoseTTAFold, in which a protein 3D structural model was generated using machine learning algorithms with amino acid sequences as the only input. Both programs can predict protein structures with near-experimental accuracy. The researchers analyzed the 3D structure of (P)RR in silico using the AlphaFold2 program and evolutionary sequence conservation profile, and investigated the functional significance of the two regions involved in the PDAC antiproliferative effect.

Research Achievement

Researchers have visualized the residue positions and evolutionary sequence conservation profiles simultaneously on the 3D structure of (P)RR. The two regions mapped onto the structural model formed a continuous surface patch comprising evolutionarily conserved hydrophobic residues.

Previous reports have demonstrated that the receptor forms a dimer, meaning that the two protein units are bound together to form one assembly unit. The generated AlphaFold2 model showed that (P)RR forms a back-to-back dimer via the extracellular domain, which explains the experimentally proven dimerization. The dimer model possessed two hand-shaped grooves with two regions of interest in the palms and an intrinsically disordered region in the fingers. Generally, an intrinsically disordered region adopts various conformations (3D shapes) under physiological conditions and can change the conformation to bind multiple partners. The surfaces of the grooves were hydrophobic, which allows for low stereospecific protein binding.

Perspectives

An open question regarding (P)RR functionality is its "promiscuity," meaning that beyond blood pressure regulation, the receptor can work on a wide range of molecules. Thus, it is conceivable that (P)RR utilizes its "hand" to catch two binding partners in a promiscuous manner and tether them closely in space to facilitate protein-protein interactions. (P)RR, in particular, is thought to catch and tether two proteins involved in Wnt/β-catenin signaling, a cell proliferation pathway linked to the pancreatic cancer development. Overall, (P)RR functions as a scaffold protein, a hub for controlling the spatial and temporal organization of molecules within a cell, and thereby the flow of cellular information.

The findings of this study will be valuable for understanding disease pathogenesis and exploring novel modalities to treat human diseases, including hypertension and cancer. Further analyses are required to experimentally characterize the interactions between (P)RR and its interaction partners.

Reference

Authors: Akio Ebihara[1,2,3,4]*, Daiki Sugihara[5], Makoto Matsuyama[6], Chiharu Suzuki-Nakagawa[1], A.H.M. Nurun Nabi[7], Tsutomu Nakagawa[1], Akira Nishiyama[8], and Fumiaki Suzuki[1]
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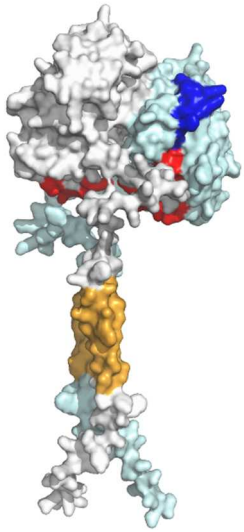
Affiliation: 1. Faculty of Applied Biological Sciences, Gifu University, Tokai National Higher Education and Research System, Japan
2. Center for Highly Advanced Integration of Nano and Life Sciences (G-CHAIN), Gifu University, Tokai National Higher Education and Research System, Japan
3. Preemptive Food Research Center (PFRC), Gifu University Institute for Advanced Study, Japan
4. Department of Chemical Engineering, Indian Institute of Technology Guwahati, India
5. Graduate School of Natural Science and Technology, Gifu University, Tokai National Higher Education and Research System, Japan
6. Division of Molecular Genetics, Shigei Medical Research Institute, Japan
7. Laboratory of Population Genetics, Department of Biochemistry and Molecular Biology, University of Dhaka, Bangladesh
8. Department of Pharmacology, Faculty of Medicine, Kagawa University, Japan

*Corresponding author's email: ebihara.akio.v9@f.gifu-u.ac.jp



Caption: The 3D shape of the (pro)renin receptor predicted by AlphaFold2 shows the presence of hand-shaped grooves allowing for multiple protein binding.

Contact

＜Research Matters＞
Akio Ebihara
Faculty of Applied Biological Sciences, Gifu University, Tokai National Higher Education and Research System
ebihara.akio.v9@f.gifu-u.ac.jp
+81-58-293-2907

＜Media Relations＞
Public Relations Group, General Affairs Division, General Affairs Department, Gifu University
kohositu@gifu-u.ac.jp
+81-58-293-3377

About Gifu University

Blessed with abundant nature and referred to as the land of seiryu (clear water), for historical and geographical reasons, the Gifu region has developed and passed down a diverse culture and technology that brought eastern and western cultures together. Having inherited these attributes, Gifu University, a constituent member of Tokai National Higher Education and Research System (THERS) trains students, who will later actively participate in society. We provide a place where students learn, explore, and contribute in an environment conducive to exploration and growth. Applying the distinguishing feature of having all undergraduate and graduate programs located on a single campus for educational and research activities, Gifu University provides education focused on training highly skilled professionals by fully utilizing a strong partnership with our THERS partner,

Nagoya University. We are committed to conducting high quality research that is the foundation of such education and to achieving internationalization rooted in the local community. The University strives to become a core hub for reinvigorating local communities through efforts such as providing local communities with the benefits derived from the above activities.
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