Revelation of protein complex function that controls cell proliferation in fruit fly wings provides insights into tumor

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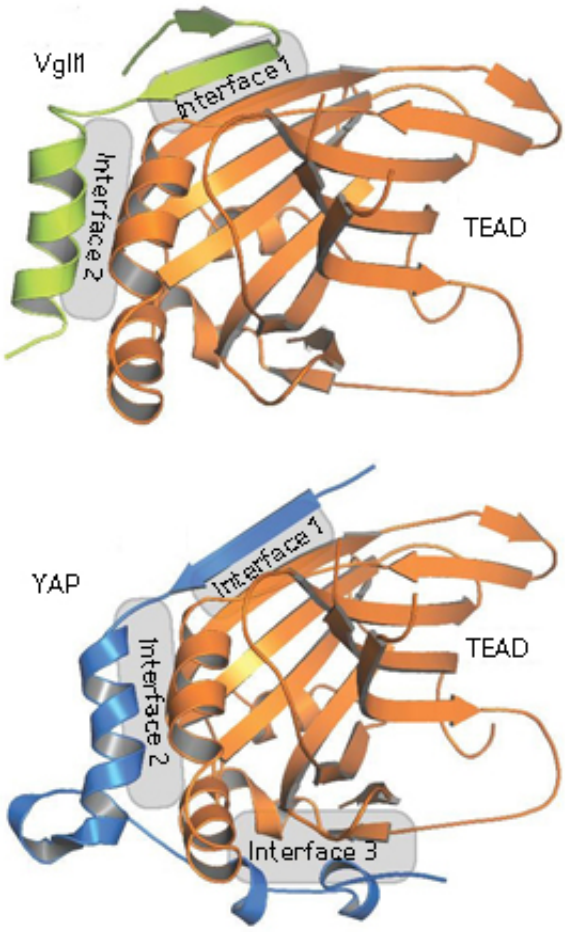

The interaction between VgII1 and TEAD (top) is mediated by two interfaces that are similar to those found in the YAP–TEAD complex (bottom). Credit: 2012 Elsevier

A team of researchers in Singapore has determined the structure of a pair of proteins that may play an important role in tumor growth and the progression of cancer. The proteins, Vestigial (Vg) and Scalloped (Sd), normally control wing development in fruit flies, but the team found they show a remarkable structural and functional similarity to the cancer-promoting proteins called YAP and TAZ.

Led by Ajaybabu Pobbati and Wanjin Hong of the A*STAR Institute of Molecular and Cell Biology, Singapore, the research team focused on these proteins because, after binding to each other, the Vg–Sd complex binds to DNA to regulate the expression of genes that control cell proliferation. The region of Vg that binds to Sd is also present in four mammalian proteins, called Vestigial-like proteins (VGII1-4). These proteins use this region to interact with the TEAD/ TEF transcription factors, the mammalian equivalents of Sd. The TEAD transcription factors also bind to YAP and TAZ. Together, they increase the expression of cell-proliferation genes that promote cancer formation.

Since little is known about the VGII proteins, the researchers used X-ray crystallography to determine the molecular structure of VGII1 bound to TEAD. Their analysis revealed that VGII1 and TEAD interact with each other in two places. The first involves structures called β-pleated sheets on VGII1 and TEAD, which bind in an antiparallel fashion, or face in opposite directions. The second consists of another structure in the VGII1 protein, called an α-helix, which sits in a groove formed by two α-helices in TEAD. The α-helices in both proteins bond to each other because of a mutual repulsion by water.

Surprisingly, Pobbati, Hong and co-workers found that both interfaces are very similar to the interfaces that mediate interactions between the TEAD and YAP proteins, despite the fact that the amino acid sequences of VGII1 and YAP bear very little resemblance to one another.

Finally, the researchers investigated the function of the VGII1–TEAD4 complex, and found that it increases expression of the IGFBP5 gene, which promotes cell proliferation. The complex also promotes anchorage-independent cell proliferation, which is one of the hallmarks of cancer. Together, these findings suggest that VGII1 may play an important role in the progression of cancer, in the same way as YAP and TAZ.

"In the future, we will be using various molecular, cellular and systems biology approaches to investigate if Vgll proteins have a definitive role in cancers," says Pobbati.

More information: Pobbati, A. V., Chan, S. W., Lee, I., Song, H. & Hong, W. Structural and functional similarity between the Vgll1-TEAD and the YAP-TEAD complexes. *Structure* 20, 1135–1140 (2012). www.cell.com/structure/retriev … ii/S0969212612001475

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