

## Clarifying the Three-Dimensional Structure of the Adenomatous Polyposis Coli-Sam68 Complex Involved in the Development of Colon Cancer

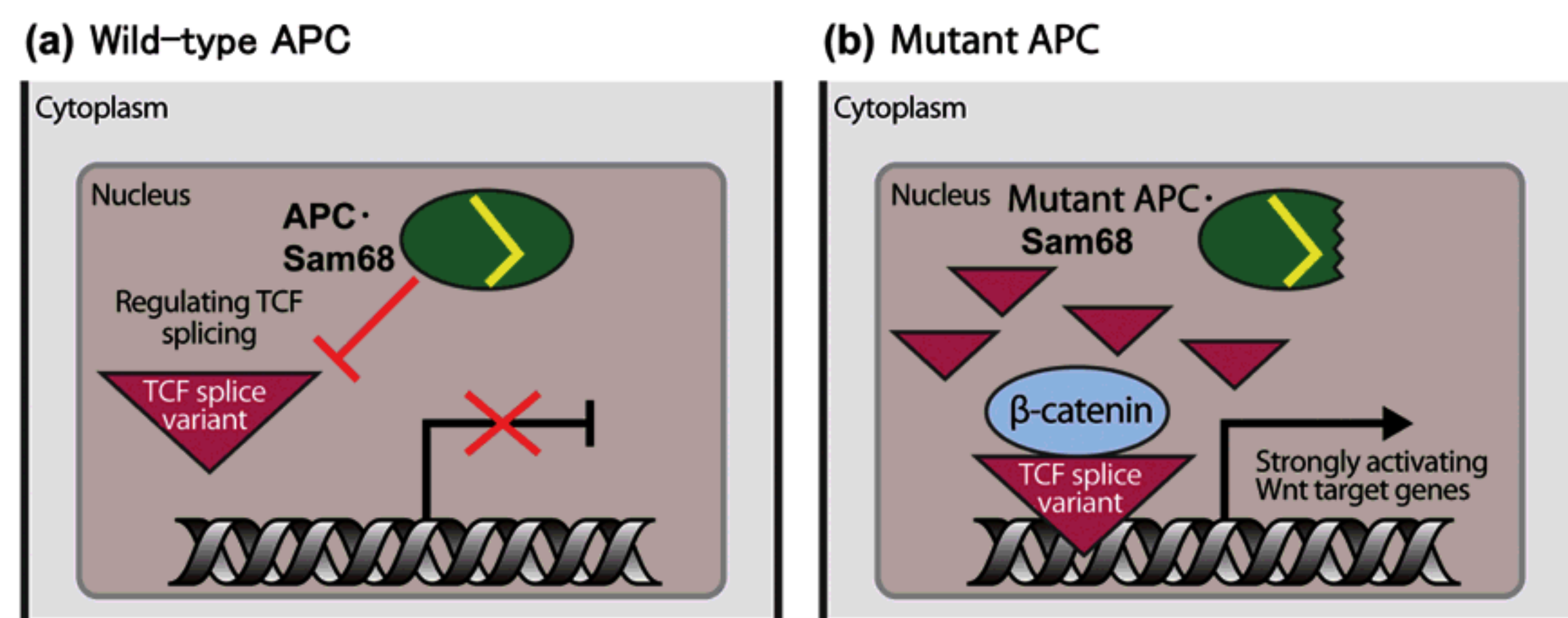
Scientists in RIKEN (Ryoji Noyori, President) succeeded in determining the structure of the functionally important part of adenomatous polyposis coli (APC), which is a protein involved in the development of colon cancer. They also succeeded in determining the 3D structure of the complex of APC and its binding factor Sam68 (APC-Sam68 complex), obtaining significant findings that will lead to the development of new strategies for the treatment of colon cancer.

The number of patients with colon cancer is increasing compared with that of patients with other cancers. There are 235,000 patients with colon cancers in Japan, according to the survey conducted by the Ministry of Health, Labour and Welfare in 2008. Moreover, colon cancer is one of the leading causes of cancer-related deaths worldwide. Effective treatments have not been found, partly because colon cancer has not been fully clarified at the molecular level. Thus far, the "APC gene" has been identified as an important gene involved in the development of colon cancer. Because mutations in this gene are found in most of the patients with

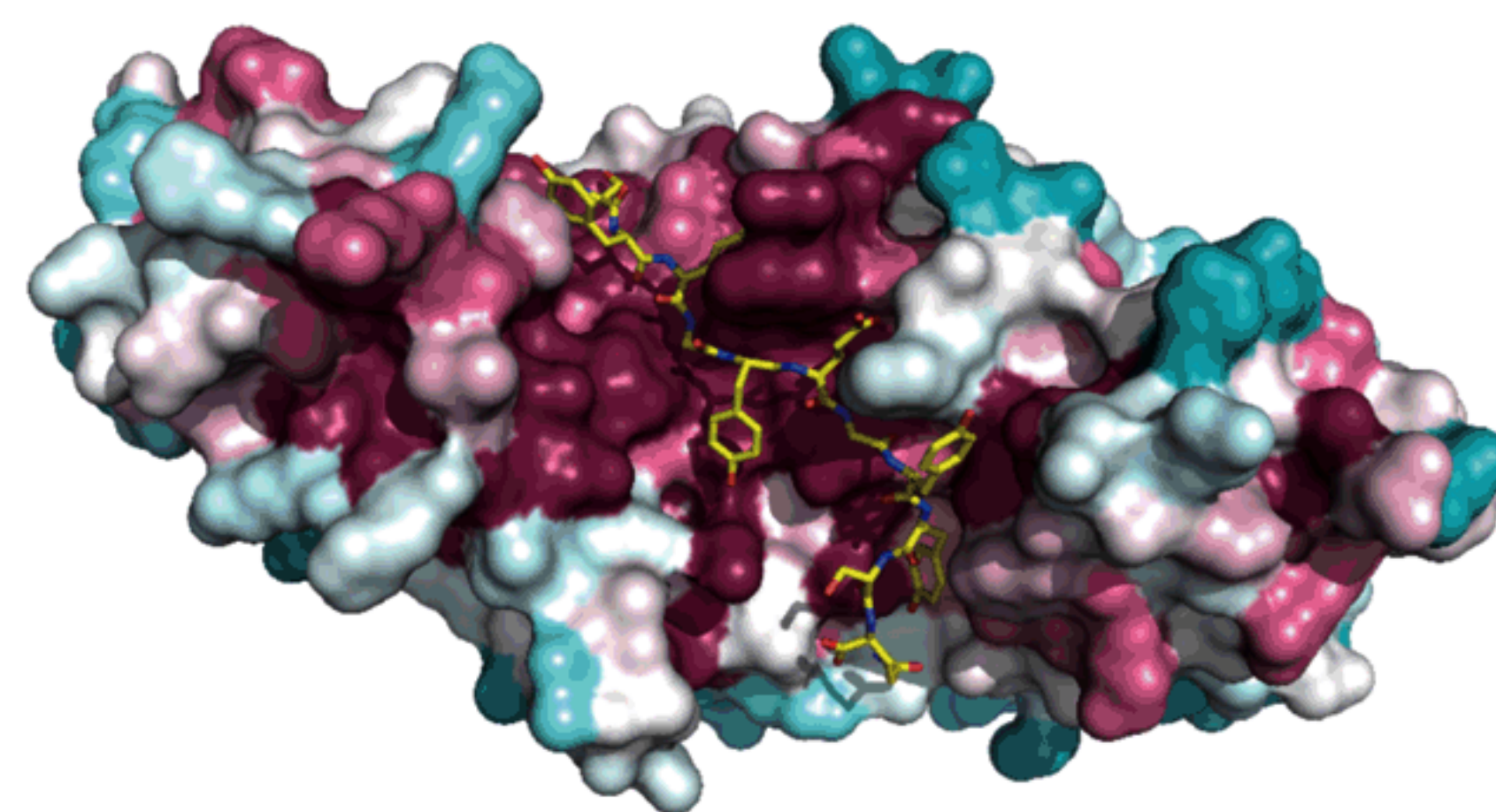
colon cancer, this gene is considered to act as a tumor suppressor gene. It is assumed that APC has a complicated higher-order structure because of its large size. Researchers have focused on the domain named the armadillo repeat (Arm) domain, which binds to many proteins. One of the proteins that binds to the Arm domain is Sam68. Recently, Professor Akiyama and his colleagues at the University of Tokyo have found that the binding of Sam68 to APC regulates the signaling that leads to the development of cancer. Then, the group at RIKEN succeeded in determining the 3D structure of the APC-Sam68 complex by X-ray crystallography and identifying the important amino acids that form the complex.

These findings will provide significant knowledge on the molecular mechanism by which mutated APC causes the development of cancers, gaining a foothold in the treatment of colon cancers. Moreover, the determination of the 3D structure of the APC-Sam68 complex will lead to the development of new anticancer drugs or new infiltration and metastasis inhibitors.

Reference: *Structure* 19 (10), 1496-1508 (2011), published online 12 October 2011



**Fig. 1 Role of APC-Sam68 complex in Wnt signal transmission**  
 (a) Wild-type APC binds to Sam68 and the resulting complex prevents the overexpression of a T-cell factor (TCF) splice variant. Thus, the activation of the target genes of Wnt is prevented, resulting in the inhibition of Wnt signaling.  
 (b) The complex of mutant APC and Sam68 promotes the overexpression of the TCF splice variant, strongly activating the target genes of Wnt, thus causing uncontrolled cell proliferation.



**Fig. 2 Crystal structure of complex of Arm domain of APC and tyrosine-rich domain of Sam68**  
 The surface of the APC molecule is colored according to the conservation of primary sequences. Dark purple and blue indicate high and low conservation, respectively. Sam68 is represented by a stick model (red, O; blue, N; yellow, C).