**Anti-apoptotic effect by the suppression of IRF1 as a downstream of Wnt/β-catenin signaling in colorectal cancer cells**

Yoichi Furukawa, et al. Oncogene. 2019 Aug;38(32)

**Presenter:** Yih-Lin Tuan                        **Date/Time:** 2020/09/17, 16:10 -17:00

**Commentator:** Chi-Wu Chiang, Ph. D. **Location:** Room 601, Med College Building

**Background:**

 Aberrant Wnt signaling has been linked to many diseases including cancer, fibrosis, and neurodegeneration diseases. One of the key mediators in this pathway is β-catenin. Consequently, degradation of β-catenin is suppressed, and the accumulated β-catenin is translocated into the nucleus, where it binds to transcription factors such as T-cell factor/lymphoid enhancer factor (TCF/LEF). The TCF/LEF family is then activated and transactivates the expression of their target genes. Previously, the authors reported that interferon-induced proteins with tetratricopeptide repeats 2 (IFIT2) was downregulated by the Wnt/β-catenin signaling, and that the suppressed expression of IFIT2 induced an anti-apoptotic effect on colorectal cancer (CRC) cells.

**Objective/Hypothesis:**

To elucidate the regulatory mechanism of IFIT2 as a downstream target of Wnt/β-catenin signaling.

**Results:**

 In this study, the authors discovered that the Wnt/β-catenin signaling destabilizes IRF1 through the ubiquitination proteasome pathway, and that reduced expression of IRF1 is involved in the down-regulation of IFIT2. In addition, they found that suppressed expression of UAF1, a component of a deubiquitinase complex of USP1, plays a vital role in the ubiquitination and subsequent degradation of IRF1 by the activation of β-catenin/TCF7L2. These data should provide a better understanding of the Wnt signaling pathway, and may contribute to the development of novel diagnostic and/or therapeutic strategy to human cancer.

**Conclusion:**

Taken together, IFIT2 is transcriptionally repressed through the downregulation of IRF1 by Wnt/β-catenin signaling in CRC cells, and that reduced activity of the USP1/UAF1 complex may play an important role in the destabilization of IRF1.

**References:**

1. Ohsugi T, Yamaguchi K, Zhu C, Ikenoue T, Furukawa Y. Decreased expression of interferon-induced protein 2 (IFIT2) by Wnt/β-catenin signaling confers anti-apoptotic properties to colorectal cancer cells. Oncotarget. 2017;8:100176–86.
2. Landré V, Pion E, Narayan V, Xirodimas DP, Ball KL. DNAbinding regulates site-specific ubiquitination of IRF-1. Biochem J. 2013;449:707–17.