Aspirin Increases the Expression of Adenomatous Polyposis Coli Protein by Suppression of IKKβ

Noboru Ashida¹, Masako Kishihata¹, Masayuki Yokode¹
¹Department of Clinical Innovative Medicine, Translational Research Center,
Kyoto University Faculty of Medicine, Kyoto, Japan

Aspirin is one of the most popularly used analgesic medicines, and it is also prescribed for most of patients suffering from atherosclerosis diseases for its anti-platelet effect. Additionally, clinical studies indicated that aspirin has protecting effect against cancer or atherosclerosis, but the mechanism in such pleiotropic effect of aspirin has not been explored. In this study, we tried to unveil the mechanism by identifying the proteins whose expression is changed by incubation with aspirin through utilizing MALDI-TOF system. Interestingly, the analysis identified the protein of Adenomatous Polyposis Coli (APC), which is clinically-proven tumor-suppressing protein and reported to regulate cell proliferation or migration, as the most up-regulated protein by aspirin in HEK293 cells. Western blots confirmed this result in HEK293 cells and human umbilical vein endothelial cells, and real-time PCR indicated it is transcriptionally regulated. Next we examined the involvement of Inhibitor of Nuclear Factor-κB Kinase β (IKKβ), an essential kinase for the activation of Nuclear Factor-κB (NFκB), in the molecular mechanism of this phenomenon, based on previous report showing aspirin specifically inhibits IKKβ. Surprisingly, the deletion of IKKβ by siRNA dramatically increases the expression of APC protein. We further tried to explore how IKKβ can regulate APC protein. Previous report indicated expression of APC protein is regulated by ubiquitination, and our proteomic analysis identified E3 ubiquitin ligase Cbl as binding protein with IKKβ. These results can be novel mechanistic insight how aspirin prevents cancer or atherosclerosis, and even a new interaction between inflammatory NFκB signalling and these diseases.