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Thesis/dissertation Title

The Role of ACC2 in Tumorigenesis: From Acute Myeloid Leukemia to Solid Tumors

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Approved Digest

The aim of my research is to study the role of Trib-COP1 and ACC2 in leukemic metabolism. I hypothesized that the downregulation of ACC2 via COP1-Trib1in AML is the key metabolic factor for their proliferation and survival. I have found that:

- The co-expression of ACC2 and COP1-Trib1 in HEK293T cells has led to the degradation of ACC2 via COP1-Trib1 complex while ACC2 mutants (Helix1 point mutant and putative ubiquitination mutant) were shown to be resistant towards the degradation via the COP1-Trib1 complex.
- The effect of COP1-Tribl mediated ACC2 degradation on cell proliferation were determined using mouse primary bone marrow cells overexpressing COP1-Trib1 with ACC2 wildtype and ACC2 mutants respectively. The results have shown that the degradation of ACC2 leads to the increase of cell proliferation while the growth of primary bone marrow cells co-expressing COP1-Trib1 and ACC2 mutants were significantly suppressed.
- The effect of ACC2 degradation via COP1-Trib1 on cell metabolism were elucidated using the flux analyzer. These results suggest that the degradation of ACC2 via COP1-Trib1 that leads to the increase in cell proliferation is due to the increase in fatty acid oxidation activity.
- Stabilization of ACC2 in COP1-Trib1 induced AML can extend the survival of mice in AML mouse model.
- Further confirmation was carried using another leukemia model, MLL-AF9. Similar findings were obtained.

- Based on the gene expression analysis, ACC2 is down-regulated in solid tumors compared to normal tissues.
- The effect of ACC2 Helix1 mutant were determined using the pancreatic cancer cell line, MIAPACA-2. The proliferation of MIAPACA-2 expressing ACC2 Helix1 mutant was significantly lower as compared to the parental cells.
- Using MIAPACA-2 xenograft mouse model, there is no tumor growth in MIAPACA-2 ACC2 Helix1 mutant xenografted mice while there were tumors in MIAPACA-2 parental mice.

Therefore, I hereby proposed that the stabilization of ACC2 protein in AML cells as well as solid tumor could suppress cell proliferation and growth in the aspect of metabolism.