Loss of CD73 promotes mutant β-catenin oncogenic activity in endometrial cancer

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Background and Hypothesis

● Patients with low grade, early-stage endometrial cancer (EC) are generally cured by surgery. However, 15-20% recur and have poor clinical outcomes.

● Exon 3 CTNNB1 (β-catenin) mutations can disrupt β-catenin degradation. They are enriched in low grade EC and associate with poor clinical outcomes. However, only half of patients with CTNNB1 mutations recur.

● Question: does CD73 loss in EC explain recurrence in β-catenin mutant tumors?

● CD73 is a cell surface enzyme that generates extracellular adenosine (Figure 1A).

● We have shown that CD73 loss associates with poor survival in EC and that extracellular adenosine rescues epithelial integrity and moves wild-type β-catenin to the membrane (Figure 1B).

● Hypothesis: CD73 sequesters mutant β-catenin to the membrane to prevent its oncogenic transcriptional activity and disease recurrence.

Results, Part I

Figure 2: CD73 loss associates with EC recurrence and nuclear localization of mutant β-catenin

Figure 3: Development of myc-tagged constructs of patient-relevant β-catenin mutants for mechanistic studies

Results, Part II

Figure 4: Loss of CD73 increases TCF/LEF activity for different human site-specific β-catenin mutants

Figure 5: Re-expression of CD73 in CD73-deficient cells decreases TCF/LEF activity for human site-specific β-catenin mutants

Figure 6: Proof-of-concept data that CD73 sequesters mutant β-catenin to the membrane

Conclusions and Future Directions

Conclusions

● CD73 predicts recurrence and β-catenin localization in patients with mutant β-catenin tumors (Part I).

● We have characterized human patient-specific β-catenin mutants (D32N, S33F, S33Y, G34R, S37C, S37F, and S45F). These mutants induce TCF/LEF transcriptional activity (Part II).

● CD73 loss increases TCF/LEF transcriptional activity for all individual β-catenin mutants (Part II).

● CD73 loss increases nuclear mutant β-catenin and decreases membranous β-catenin/E-cadherin interactions (Part II).

● CD73 likely protects against EC recurrence by sequestering mutant β-catenin to the membrane with E-cadherin (Figure 7).

Future Directions

● Perform RNA-seq to identify transcriptional targets of specific mutants in the presence and absence of CD73.

● Perform cellular fractionations to determine if CD73 can sequester various forms of mutant β-catenin to the membrane.

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