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Pattern of PIK3CA co-alterations in endometrial cancer.

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Purpose

Aberrant activation of the PI3K pathway drives tumor proliferation and survival. The aim of this study was to identify PIK3CA pathway activation patterns unique to endometrial cancer by profiling functional mutational frequencies and co-mutation with PTEN and TP53.

Methods

Molecular profiles of 1,180 unique cancer (endometrial, breast, lung and colorectal) patients' formalin-fixed paraffin embedded (FFPE) tissue samples were analyzed for co-alterations with PIK3CA mutations. Samples were evaluated using a 323 gene NGS panel utilizing the QIAseq targeted DNA chemistry. The Fisher's exact test was used for a comparison of frequencies between two groups.

Results

The most frequent PIK3CA mutations are found in the kinase domain (KD) in both endometrial and breast cancers; 42.4% in endometrial and 55.4% in breast. Hotspot p.H1047 made up 64.3% and 84.4% of KD mutations, in endometrial and breast cancer respectively. The same preference for KD and hotspot p.H1047 mutations was not observed in lung or colorectal cancers, where helical domain alterations were the predominant PIK3CA mutations. There were significantly more PIK3CA adaptor binding domain mutations compared to other tumor types: in endometrial cancer 21.2%, breast 3.6% (p<0.0001), lung 8.8% (p=0.004), and colorectal 9.9% (p=0.0027). Additionally, there were significantly more PTEN co-mutations in endometrial cancer (58.6%) compared to breast 7.2% (p<0.0001), lung 5.5% (p<0.0001), and colorectal 8.2% (p<0.0001). Among PIK3CA-mutated endometrial patients with a co-mutation in PTEN, there were significantly fewer TP53 mutations when compared to those with no PTEN co-mutation (17.2% vs. 70.7%; p<0.0001).

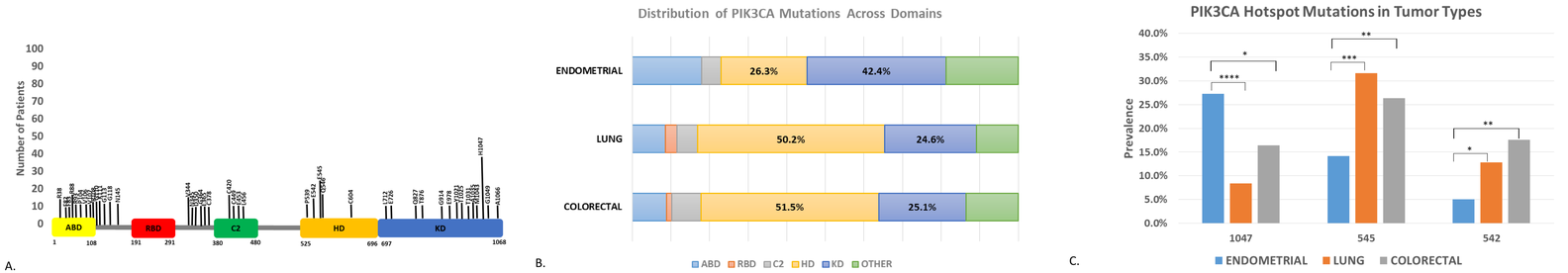

Figure 1. Distribution of domain-specific PIK3CA mutations. A) Peaks indicate the number of patients in the 99 endometrial cancer patients cohort that have the specific mutation and boxes represent functional domains (Adaptor binding domain, Ras binding domain, C2 domain, helical domain, and kinase domain). B) Distribution of domain-specific PIK3CA mutations in endometrial cancer (n=99 patients) compared to lung (n=452 patients) and colorectal (n=342 patients). C) The prevalence of hotspot PIK3CA mutations (1047, 545 and 542) in endometrial (n=99), lung (n=452) and colorectal (n=342) cancers. Statistical analysis was performed using Fisher's exact test (****, p < 0.0001).

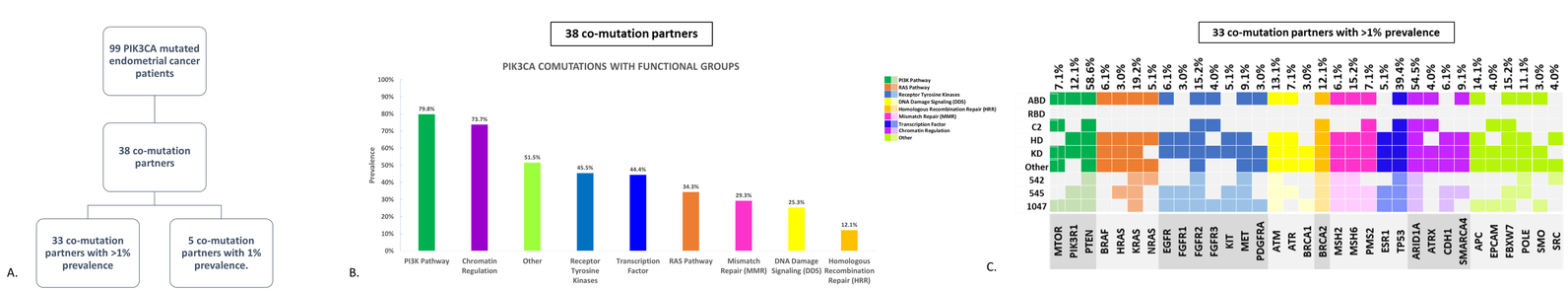

Figure 2. PIK3CA co-mutations in endometrial cancer. A) Overview of the study. B) Prevalence of PIK3CA co-mutations with 38 unique partners in various functional groups. C) The heatmap shows specific PIK3CA co-mutations distributed over its various domains (ABD, RBD, C2, HD, KD, other), hotspots (542, 545, 1047) and co-variant functional groups. Percentages (%) are the overall prevalence of the specific PIK3CA co-mutations. Note, only 33 out of 38 PIK3CA co-mutation partners where selected for the heatmap analysis. The cut off for selection was >1% (>1 patient) prevalence.

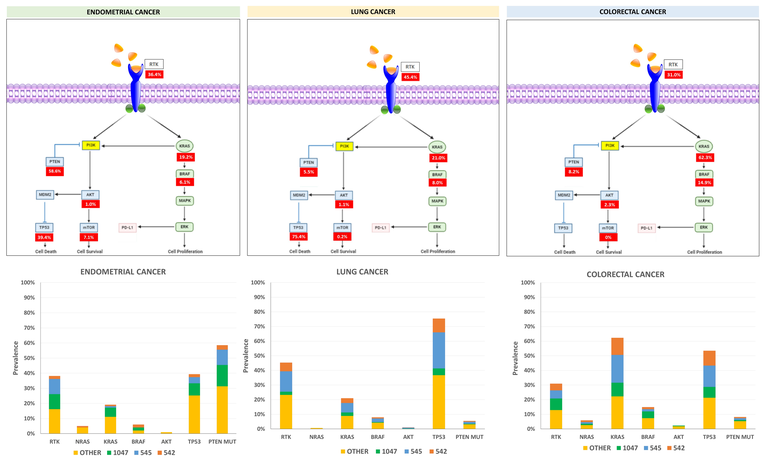

Figure 3. Selective hotspot mutations are associated with distinct patterns of pathway activation. Overview of cell signaling mediated by the tyrosine kinase receptors (RTKs). PI3K/AKT and RAS/MAPK signaling pathways are interconnected and their abnormal activation promotes cell growth, proliferation, survival, and other hallmarks of cancer. Percentages (%) are the prevalence of PIK3CA co-mutations (red) PIK3CA mutations.

Key Points

- PIK3CA mutations and co-mutations distribute very differently with respect to prevalence and domain specificity. Unlike lung and colorectal cancers, the KD is the domain of preference for mutations in endometrial cancer. Hotspot p.H1047 is the main contributor to KD mutations in endometrial cancer.
- In endometrial cancer, PTEN is more frequently mutated upon PI3K/AKT pathway hyperactivation, abrogating its normal inhibitory effect on PI3K resulting in increased cell proliferation and survival. When PTEN is not mutated, alterations downstream of AKT, such as TP53 mutations, may serve as alternative cell survival regulators.
- Cohort studies, like the present retrospective study, aid in understanding the mutation profile and identifying clinically actionable markers. This study provides insight into the patterns of molecular alterations present within PIK3CA-mutated patients, which could be instrumental in stratifying patient population.