Molecular Profiling Reveals Distinct Molecular Landscapes in 545 Cases of Triple Negative Endometrial Cancer

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Abstract

Objective: The term “triple negative” has traditionally been used to characterize a subtype of breast cancer that lacks estrogen, progesterone, and HER2 receptor expression. Triple negative breast cancers behave aggressively, are associated with poor prognosis, and have limited treatment options. It is unknown whether similar phenotypes found in other cancer types, such as endometrial cancer, harbor similar molecular alterations and prognosis. We sought to compare genetic and molecular features of triple negative endometrial cancers (TNEC) with non-TNEC to identify possible therapeutic targets. Methods: A total of 3133 endometrial cancer cases were evaluated by Caris Life Sciences (Phoenix, AZ) from March 2011 to July 2014 by multiplex platform, which included sequencing (Sanger or NGS), protein expression (IHC), and for gene amplification (CISH or FISH). The molecular profiles of 545 TNEC and 2162 non-TNEC were identified based on expression profiles and compared using Fisher exact tests. Results: The frequency of TNEC in our cohort was 17%. Of 545 TNEC cases, 13% were endometrioid, 22% serous, 26% carcinosarcoma (MMMT), 7% clear cell, and 22% other Table 1 compares molecular and genomic alterations between TNEC and non-TNEC. Compared to non-TNEC, TNEC had more frequent TP53 and BRCA1 mutations and more frequent alterations of the DNA synthesis pathway with higher TOP2A, TOP2B, TS, and ERBB2 expression. Immune modulatory, FGFR and Wnt pathways were less often altered in TNECs as evidenced by lower PD1 expression, fewer FGFR2 and fewer CNTN81 mutations, respectively. PIK3CA/MTOR pathway alterations were less common in TNEC with fewer PIK3CA, PTEN, and AKT mutations. Finally, expression of ALK and TE3 was less common in TNEC compared to non-TNEC. Conclusion: TNEC appears to have a distinct molecular background from non-TNEC. Differences were seen in pathways involved in DNA repair, DNA synthesis, immune modulatory function, and the PIK3CA/MTOR pathway. Further studies are warranted to validate the clinical applicability of these findings.

Results

Fig. 1. Comparison of molecular differences between TNEC and non-TNEC

Fig. 2. Comparison of genetic differences between TNEC and non-TNEC

Table 1. Comparison of genomic differences between TNEC and non-TNEC

Table 2. Comparison of genomic differences between TNEC and non-TNEC

Table 3. Summary of TNEC and non-TNEC molecular signatures

Results (continued)

Conclusions

Fig. 2. Comparison of genetic differences between TNEC and non-TNEC

Table 3. Summary of TNEC and non-TNEC molecular signatures

- We identified several pathways that warrant further exploration in a large cohort (>545) of triple negative endometrial cancers. There is a significantly higher frequency of TP53 mutations in TNEC, suggesting a more aggressive subtype and inferior outcomes.
- Greater heterogeneity in the DNA synthesis pathway was noted in TNEC with higher TOP2A, TOP2B, TS, and ERBB2 expression, which may be associated with reduced apoptosis.
- Proteomic data indicate that TNEC is linked with some well-characterized molecular pathways. A combination of these pathways and other potential mechanisms will be explored in future studies.
- Incorporation of both molecular and clinical profiling in future TNEC clinical trials will be needed to determine if the triple negative phenotype has therapeutic or prognostic significance in endometrial cancer.

References