"Triple negative" has traditionally been used to characterize a subtype of breast cancer that lacks estrogen, progesterone, and HER2 receptor expression. They are aggressive cancers with limited treatment options. In certain cases, the term refers to a molecular phenotype found in other cancer types like endometrial cancer, harbor similar molecular alterations and prognosis. We aim to compare molecular features of triple negative endometrial cancers (TNEC) and triple negative breast cancers (TNBC) to reveal unique expression profiles.

Objectives: Triple negative breast cancers behave more aggressively than other subtypes, and lack of neoadjuvant therapy is poor. Similar to breast cancer, TNEC tumors were identified and evaluated. Patients evaluated were from 2010 - 2011. Patients were evaluated by using M13-linked PCR primers directed to specific target sequences. The results are confirmed by formalin-fixed paraffin-embedded tumor samples using the Illumina MiSeq platform. Specific regions of DNA and RNA were sequenced using the TruSight Sequence Capture Kit.

Methods: A total of 3133 endometrial cancer samples were evaluated by Caris Life Sciences (Phoenix, AZ) from 2010 to 2011 and 2014 by multiplatform profiling, which included a combination of sequencing (Sanger or NGS), protein expression (IHC), and/or gene amplification (CISH or FISH). 545 TNEC and 2049 TNBC were identified based on reported pathology and compared using Fisher's exact test.

Results: Compared to an incidence of 15-20% TNBC in breast cancer, 17% (545/3133) TNEC was seen in our cohort, of which 13% were endometrioid, 22% serous, 26% carcinosarcoma, 7% clear cell, and 22% other. Compared to TNBC, TNEC showed 1.9x more mutations per case while TNBC showed 1.2 mutations per case. As shown in the Table, AR expression is lower in TNEC than TNBC. TP53 mutation was common in both but more frequent in TNBC. BRCA1/2 mutation rates were similar, low MGMT and ERCC1 were more common in TNEC, suggesting increased aberrant DNA repair. DNA synthesis protein expression was higher in TNEC and BRCA1/2 mutations were more common in TNEC suggesting immune pathophysiology involvement. PIK3CA/TM10s, MMR, and Wnt pathways were more involved in TNEC with greater PTEN, PIK3CA, FBXW7, RAS, and CTNNB1 mutations.

Conclusion: Our study reveals significantly higher overall mutation rates in TNEC than in breast cancer and specifically higher activations of multiple molecular pathways including PIK3CA/TM10s, MMR, and Wnt. Further studies are warranted to validate these findings in clinical trials.

Results (continued)

• Triple negative breast cancers behave aggressively, are associated with a poor prognosis, and have limited treatment options
• Less than 15% of cancers have the triple negative phenotype
• It is unknown whether similar phenotypes found in other cancer types, such as endometrial cancer, harbor similar molecular alterations and prognosis
• We aim to compare molecular and clinical features of triple negative endometrial cancers (TNEC) and triple negative breast cancers (TNBC).

Figure 1. Comparison of molecular differences between TNEC and TNBC

Figure 2. Comparison of molecular differences between TNEC and TNBC

Table 1. Molecular differences between TNEC and TNBC

Table 2. Mutation differences between TNEC and TNBC

Table 3. Summary of TNEC and TNBC molecular signatures

Conclusions

• We identified unique molecular and genomic differences between a large cohort of triple negative endometrial and triple negative breast cancers.
• The incidence of triple negative endometrial cancer (17%) in our cohort was similar to reported incidence of triple negative breast cancer (15-20%) in the literature.
• Compared with TNBC, TNEC showed 1.9x more mutations per case while TNBC showed 1.2 mutations per case.
• M13-linked primers were used for sequencing.
• TP53 mutation was common in both but more frequent in TNEC.
• We compared genomic and molecular features of triple negative cancers.

References