Novel Fusion Genes as Diagnostic Biomarkers for High-grade Serous Ovarian Carcinoma

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Technology description

Ovarian cancer is the 5th leading cause of cancer death in woman with approximately 70% of deaths is due to the high-grade serous carcinoma (HG-SC) subtype, which is typically detected at advanced stages due to lack of early screening tools. HG-SC is characterized by a high degree of heterogeneity among tumors and massive genome rearrangements, and recurrent mutations that are specific only to HG-SC have been difficult to identify, presumably due to the high heterogeneity among tumors. Dr. Laising Yen and his team identified CDKN2D-WDFY2 as a cancer-specific and inter-chromosomal fusion gene presented in 20% of HG-SC tumors, and this fusion gene has three key features:
1) It is by far the most frequent gene recombinant event found in this highly heterogeneous disease;
2) It is not present in the non-cancerous ovaries or fallopian tubes;
3) The exact same RNA junction is observed in the fusion transcript across patient samples, suggesting that this mutation leads to a specific aberrant protein function.
In a follow-up study, the researchers identified another HG-SC cancer-specific fusion gene, BCAM-AKT2, which leads to the translation of a constitutively activated AKT2 fusion kinase. The BCAM-AKT2 fusion is present in 7% of HG-SC samples studied, still a significant frequency considering the highly heterogeneous nature of this malignancy.
Publications
- CDKN2D-WDFY2 Is a Cancer-Specific Fusion Gene Recurrent in High-Grade Serous Ovarian Carcinoma. Kannan K, Coarfa C, Rajapakshe K, Hawkins SM, Matzuk MM, Milosavljevic , Yen L. PLoS Genet. 2014 Mar 27;10(3):e1004216. - Recurrent BCAM-AKT2 fusion gene leads to a constitutively activated AKT2 fusion kinase in high-grade serous ovarian carcinoma. Kannan K, Coarfa C, Chao PW, Luo L, Wang Y, Brinegar AE, Hawkins SM, Milosavljevic A, Matzuk MM, Yen L. Proc Natl Acad Sci U S A. 2015 Mar 2. [Epub]

Application area

- The presence of CDKN2D-WDFY2 fusion gene was identified by RNA sequencing and has been validated by RT-PCR in 60 HG-SC cancer samples at a frequency of 20%. The same fusion transcript was also detected in OV-90, an established high-grade serous type cell line.

- The BCAM-AKT2 fusion gene was identified and validated by applying similar approaches in the same set of clinical samples above, and in vitro functional studies suggest that BCAM-AKT2 is oncogenic.

Advantages

- The above fusion genes can be used as novel clinical diagnostic markers that are specific for HG-SC with high frequencies.
- The fusion RNA can be reliably detected by RT-PCR, and it might be present in circulating cancer cells or in local body fluids, which makes non-invasive detection possible. - The fusion gene, fusion RNA, or fusion protein detection can yield a clear ΓÇ£yes or noΓÇØ result for early detection of a substantial fraction of HGSC. This advantage eliminates the need for thresholds or cut-off levels which is a common problem associated with biomarkers that are over-expressed but not cancer-specific.

Institution

Baylor College of Medicine

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com