Année de publication : 2018


**Medullary Breast Carcinoma, a Triple-Negative Breast Cancer Associated with BCLG Overexpression.**
*The American journal of pathology*: DOI: S0002-9440(17)31226-9

**Résumé**

Medullary breast carcinoma (MBC) is a rare subtype of triple-negative breast cancer with specific genomic features within the spectrum of basal-like carcinoma (BLC). In this study of 19 MBCs and 36 non-MBC BLCs, we refined the transcriptomic and genomic knowledge about this entity. Unsupervised and supervised analysis of transcriptomic profiles confirmed that MBC clearly differs from non-MBC BLC, with 92 genes overexpressed and 154 genes underexpressed in MBC compared with non-MBC BLC. Immunity-related pathways are the most differentially represented pathways in MBC compared with non-MBC BLC. The proapoptotic gene BCLG (official name BCL2L14) is by far the most intensely overexpressed gene in MBC. A quantitative RT-PCR validation study conducted in 526 breast tumors corresponding to all molecular subtypes documented the specificity of BCLG overexpression in MBC, which was confirmed at the protein level by immunohistochemistry. We also found that most MBCs belong to the immunomodulatory triple-negative breast cancer subtype. Using pan-genomic analysis, we found that MBC harbors more losses of heterozygosity than non-MBC BLC. Our observations corroborate the notion that MBC remains a distinct entity that could benefit from specific treatment strategies (such as deescalation or targeted therapy) adapted to this rare tumor type.


**Clinical potential of circulating tumour DNA in patients receiving anticancer immunotherapy.**
*Nature reviews. Clinical oncology*: DOI: 10.1038/s41571-018-0074-3

**Résumé**

Considerable interest surrounds the use of immune-checkpoint inhibitors in patients with solid tumours following the demonstration of the impressive clinical efficacy of anti-programmed cell death protein 1 and anti-programmed cell death 1 ligand 1 antibodies in several tumour types. However, the emergence of unexpected tumour response patterns, such as pseudoprogression or hyperprogression, might complicate the management of patients receiving these agents. Analysis of circulating tumour DNA (ctDNA) has been shown...
to have prognostic value by enabling the detection of residual proliferating disease in the adjuvant setting and estimation of tumour burden in the metastatic setting, which are key stratification biomarkers for use of immune-checkpoint inhibition (ICI). Furthermore, examinations of ctDNA for genetic predictors of responsiveness to immunotherapy, such as mutations, tumour mutational load, and microsatellite instability provide a noninvasive surrogate for tumour biopsy sampling. Proof-of-concept reports have also demonstrated that quantitative changes in ctDNA levels early in the course of disease are a promising tool for the assessment of responsiveness to ICI that might complement standard imaging approaches. Other applications of this technology are also currently under investigation, such as early detection of resistance to immunotherapy and characterization of mechanisms of resistance. The aim of this Review is to summarize available data on the application of ctDNA in patients receiving immunotherapy and to discuss the most promising future directions.


[MBD4 inactivation induces a new mutator phenotype in cancers].
Bulletin du cancer : DOI : S0007-4551(18)30193-0

Résumé


Outlier response to anti-PD1 in uveal melanoma reveals germline MBD4 mutations in hypermutated tumors.
Nature communications : 1866 : DOI : 10.1038/s41467-018-04322-5

Résumé

Metastatic uveal melanoma is a deadly disease with no proven standard of care. Here we present a metastatic uveal melanoma patient with an exceptional high sensitivity to a PD-1 inhibitor associated with outlier CpG>TpG mutation burden, MBD4 germline deleterious mutation, and somatic MBD4 inactivation in the tumor. We identify additional tumors in The Cancer Genome Atlas (TCGA) cohorts with similar hypermutator profiles in patients carrying germline deleterious MBD4 mutations and somatic loss of heterozygosity. This MBD4-related hypermutator phenotype may explain unexpected responses to immune checkpoint inhibitors.
Publications de l’équipe
Génomique et biologie des cancers du sein héréditaires