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Early breast cancers are infiltrated by oligoclonal T cells population highly concentrated relative to the blood

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BACKGROUD: The immunogenicity of some human tumors towards T lymphocytes is well established and this motivated the usage of anti-tumoral immunotherapies. Recently, encouraging results have been achieved with immune system checkpoint inhibitors in tumors like melanoma, lung cancer and bladder cancer. Usage of immune checkpoint inhibitors in the domain of breast cancer (BC) is less advanced and it has been suspected that these tumors are poorly immunogenic.

METHODS: Repertoire of tumor infiltrating T cells were evaluated in 17 early BC by a genetic approach. RNA was extracted and reverse transcribed from paraffin embedded formalin fixed tumor tissues. A small random sequence was integrated into the cDNA and used as a unique molecular identifier (UMI) which make each molecule distinct. cDNA encoding for T cell receptor β chains (TCRβ) including the CDR3 highly variable region was then amplified and sequenced using high throughput sequencing. TCRβ sequences were aligned using IMGT/HighV-QUEST and diversity of the T cell repertoire was assessed. Usage of UMIs during this procedure strongly improved accuracy of the analysis by avoiding bias inherent to the sequencing library construction and allowed absolute quantification of the TCRβ chains normalized with the RPP30 housekeeping gene. For 3 patients, same procedure was applied on blood circulating T cells collected few days before tumor resection. Analysis was also realized on samples from 3 normal tissues from breast reduction surgery.

RESULTS: T cell infiltration is strongly variable from one tumor to another. The lowest infiltrated tumor has 5 TCRβ chains/10^3 RPP30 copies compared to 2498 TCRβ chains/10^3 RPP30 for the more infiltrated one. T cell repertoire analysis revealed that infiltrated T cell correspond to oligoclonal populations. We observe 3 different clonotypes in the smaller repertoire and 74 in the largest one. 16/17 tumors had at least one clonotype reaching 10% among T cells and highest observed frequencies ranged from 7% to 80%. Normal breast tissues were infiltrated by a more diverse repertoire. 130 to 368 clonotypes were identified in those tissues and their highest measured frequency was 2%. For 3 patients, frequencies of most prevalent clonotypes in the tumor were compared to the frequencies of the same clonotypes in the blood before tumor resection. this comparison revealed that amplified tumor infiltrating T clonotypes were 250x to >34000x more concentrated in the tumor environment than in the blood.

CONCLUSIONS: Some early BC are infiltrated by oligoclonal T cells population highly concentrated in the tumor environment relative to the blood. This is a strong argument in favour or tumor immunogenicity and brings rationale for the usage of immune checkpoints inhibitors in selected early BC. Fine quantitative T cell repertoire analysis allow to distinguish 3 tumors categories: (1) tumors without T cell infiltration, (2) tumors with a high T cell infiltration composed of a small T cell repertoire, and (3) tumors with a high T cell infiltration composed of a wider repertoire. We hypothesise that distinction among this BC subgroups could be used as a predictive biomarker for immune checkpoints inhibitors effectiveness.