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SEARCHING FOR BIOMARKERS TO IMMUNE CHECKPOINT INHIBITORS TREATMENT RESPONSE IN LUNG ADENOCARCINOMA: A THE CANCER GENOME ATLAS EXPLORATORY ANALYSIS

CATEGORIA DO TRABALHO: PESQUISA

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Few biomarkers accurately patients with a high clinical response to immunotherapeutic drugs in lung cancer. Patients with hypermutated - high tumor mutational burden (TMB) tumors demonstrated better response rates of immune checkpoint inhibitors (ICI) in several studies in the past years. However, just as PD-L1 and CTLA4 demonstrated a good and escalated use in clinical patients predictive treatment response, TMB seems to be drifting to become another non-highly sensitive biomarker if used alone. This study aims to search for biomarkers related to a more immunogenic tumoral profile, which could lead to a better understanding of ICIs immunotherapy treatment sensitivity gain or loss and be used as surrogate markers in the ion of candidate patients. Lung adenocarcinoma (LUAD) cohort available in The Cancer Genome Atlas (TCGA) public dataset was downloaded the genomic data commons data portal. The RNA-seq gene expression profile clinical datasets for the LUAD dataset were accessed and acquired with the aid of the R platform (TCGAbiolinks package) for analysis. Mutations in driver genes and genes associated with gain and loss of sensibility to ICIs and tumor inflammatory profile were analyzed and compared according to their hypermutation status (>10 Mutations/Mb = hypermutated), smoking habit, and alteration in TP53 gene alone and combined. The gene expression associated with immune system cell activation, such as CD4/CD8 ratio, CTLA4 IFNG, and GZMA demonstrated an increased expression profile change in the hypermutated group smoking habit and mutant TP53 ($p<0,05$). In the analyzed cohort, 3% (n=15) exhibited mutations in JAK2; and a decreased IFNG gene expression $p=0.0095$), both determinants for sensitivity loss to immunotherapeutic drugs. ARID1A alterations account for 4% (n=25) and those tumors demonstrated increased CTLA4 expression $p=0,0059$, a direct target for ICIs. Hypermutated status, TP53 alterations, and smoking habits are associated with a more immunogenic expression profile alone, leading to even higher key molecules expression profile change when combined. Additionally, alterations in the ARID1A and JAK2 generated expression profile changes in immune checkpoint target molecules, suggesting that these changes may modulate the immunotherapeutic treatment response providing sensitivity gain or loss, depending on the affected gene.

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ANÁLISE DO POTENCIAL PRÓ TUMORAL DE NEUTRÓFILOS EM MODELO DE CULTIVO CELULAR 3D DE GLIOBLASTOMA

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As células imunes são importantes constituintes do microambiente tumoral, possuindo um papel extremamente relevante na comunicação e interação intercelular e podendo favorecer a progressão tumoral. Dentre as células presentes, os neutrófilos, leucócitos que atuam na primeira linha de defesa contra microrganismos, apesar de não serem os mais abundantes, estudos demonstram que seu papel no microambiente tumoral pode ter sido subestimado. Eles apresentam plasticidade funcional, alterando-se fenotipicamente de acordo com fatores proporcionados pelo meio: possuem um espectro de ativação antitumoral (N1) e pró-tumoral (N2). A presença dessas células no microambiente tumoral é essencial para a formação de um sítio propício para o desenvolvimento das células tumorais. No glioblastoma, tumor cerebral mais agressivo e mais comum, foi demonstrado importante infiltrado neutrofílico, surgindo questionamentos sobre a interação entre essas células. Ademais, modelos de cultivo 3D vem sendo utilizados devido à sua capacidade de mimetizar condições encontradas clinicamente, como o acesso a nutrientes e pontos de hipoxia.Considerando isso, esse estudo visou avaliar o potencial pró-tumoral de neutrófilos em cultivo com glioblastoma em cultura celular bidimensional e tridimensional. Para isso, foram realizados testes in vitro com linhagem celular de glioma