Tryptophan catabolism differentiates breast cancer patients from healthy controls but does not predict outcome

C.E. Onesti¹, F. Boemer², C. Josse³, S. Leduc², C. Poulet³, V. Bours³, G. Jerusalem¹

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Background: Indoleamine 2,3 dioxygenase (IDO) catalyzes the conversion of tryptophan (Trp) into kynurenine (Kyn), an immunosuppressive metabolite involved in T regulatory cell differentiation. IDO is expressed in many cancer types, including breast cancer (BC), but its association with prognosis is controversial. Here we analyze Kyn/Trp ratio, known as a surrogate indicator of IDO activity, in BC patients and in healthy controls.

Methods: We prospectively enrolled 350 subjects, i.e. CTRL or BC patients (pts). All the subjects underwent a blood sample withdrawal at BC diagnosis or the day of the screening mammography for CTRL. After centrifugation, plasma was collected and stored at -80°C. Kyn and Trp were determined on a TQ5500 tandem mass spectrometer after chromatographic separation. Statistical analysis was performed with SPSS v24 software.

Results: We enrolled 146 CTRL and 204 stage I-III BC (85.1% ductal, 11.4% lobular, 3.5% other). The median age was 56 years (range 26-86). Overall, 29.7% of the cases were Luminal A, 44.1% Luminal B, 6.9% HER2-enriched and 19.3% triple negative. All the pts received surgery, 126 NAC with 43 pathological complete response (pCR), and 43 adjuvant chemotherapy. We observed significant higher Kyn, Trp and their ratio in CTRL vs BC (Table). We enrolled 146 CTRL and 204 stage I-III BC (85.1% ductal, 11.4% lobular, 3.5% other). The median age was 56 years (range 26-86). Overall, 29.7% of the cases were Luminal A, 44.1% Luminal B, 6.9% HER2-enriched and 19.3% triple negative. All the pts received surgery, 126 NAC with 43 pathological complete response (pCR), and 43 adjuvant chemotherapy. We observed significant higher Kyn, Trp and their ratio in CTRL vs BC (Table). We observed a higher Kyn/Trp ratio in estrogen receptor (0.042 ± 0.016 vs 0.038 ± 0.012, p = 0.04) and progesterone receptor (0.041 ± 0.016 vs 0.038 ± 0.012, p = 0.048) negative pts, and a lower ratio for lobular histology (0.033 ± 0.008 vs 0.039 ± 0.014 in ductal vs 0.039 ± 0.008 in other, p = 0.005). PCR was associated with higher Kyn (1.81 ± 0.47 μM/L vs 1.65 ± 0.59 μM/L, p = 0.039), but not with Kyn/Trp ratio (p = 0.367). Moreover, Kyn/Trp ratio was not predictive of disease free survival (p = 0.194) and breast cancer specific survival (p = 0.509). Table. Kyn and Trp in CTRL and BC pts.

Conclusions: Kyn/Trp ratio is not predictive of pCR and outcome. Kyn, Trp and their ratio are higher in CTRL than in BC pts. The concomitant reduction of Kyn and Trp suggest a rapid catabolism in presence of BC. Further studies, with the dosage of downstream metabolites are necessary to confirm it.

Legal entity responsible for the study: Laboratory of Human Genetics, GIGA Institute, Liege, Belgium.

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Table: 55P

<table>
<thead>
<tr>
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<th>CTRL</th>
<th>BC</th>
<th>P value</th>
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<tr>
<td>Kyn (μM/L)</td>
<td>1.951 ± 0.708</td>
<td>1.770 ± 0.535</td>
<td>&lt;0.0001</td>
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<tr>
<td>Trp (μM/L)</td>
<td>48.8 ± 14.2</td>
<td>44.6 ± 11.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Kyn/Trp</td>
<td>0.041 ± 0.019</td>
<td>0.038 ± 0.013</td>
<td>0.019</td>
</tr>
</tbody>
</table>

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