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TRANSIENT DOWNREGULATION OF INDOLEAMINE 2,3-DIOXYGENASE (IDO) IS CRITICAL FOR BLADDER CANCER CELL INVASION

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The most common form of human bladder cancer is non-muscle invasive, however, half of these cases progress to a muscle-invasive, which ultimately leads to metastasis and cancer-specific death. Indoleamine 2,3-dioxygenase (IDO) is an enzyme induced strongly by INF-gamma that has been recognized as an immunomodulatory molecule since it was described in the placenta protecting embryos tissue against maternal immune attack. A growing body of evidence suggests that IDO is expressed in tumors, enabling cancers to evade immune surveillance. Moreover, IDO has presented nonimmunological effects in some tumors. Recently, we demonstrated that IDO expression is suppressed by TGF-beta in bladder cancer cells, an important inductor of cancer invasiveness. Here, we raised the hypothesis that IDO is involved in the bladder cancer cell invasion process. IDO activity promotes tryptophan breakdown, increasing kynurenines in the microenvironment. Among the IDO-activated pathways
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there is the aryl hydrocarbon receptor, activated by kynurenines, and the GCN2, a pathway sensitive to tryptophan depletion. The
analyze the expression of IDO and its pathways AHR and GCN2 during muscle-invasive bladder cancer cell invasion, and to ver
gamma-inducted IDO affects cell invasion. T24 cells underwent starvation for 24h and then were seeded in Matrigel/transwell sys
hours, in order to separate invasive cells (IC) from non-invasive cells (NIC). The IC cells, which migrated to transwell, were trypsiniz
RNA was extracted. Concomitantly, Matrigel-retained cells were isolated as NIC, and total RNA was extracted. In the second phas
experiment was performed, however, IC and NIC cells were collected and subcultivated in RPMI 1640 10% FCS for 18 days. Finally,
phase, INF-gamma-treated T24 cells and non-INF-gamma-treated T24 cells were seemed in the Matrigel/transwell system to a
migration rate after 24h. Real-time PCR for IDO, CYP1A1 (AHR activation marker), and CHOP (GCN2 activation marker) was carri
expression was lower in IC versus NIC (relative expression 1.02 ± 0.27 vs. 6.15 ± 1.60, p<0.05). In addition, expression of CYP1A1
also decreased in IC (relative expression of CYP1A1 of 1.00 ± 0.12 in IC vs. 3.15 ± 0.46 in NIC, p<0.05; and relative expression o
1.06 ± 0.23 in IC vs. 0.36 ± 0.06 in NIC, p<0.05). The culture of IC and NIC over a long time (18 days) showed that the differ
expression of IDO, CYP1A1 and CHOP previously found disappeared. The treatment with INF-gamma significantly increased the ex
IDO in total T24 cells (60X), demonstrating T24 cells responsiveness to INF-gamma. The Matrigel/transwell analysis showed that the
with INF-gamma significantly reduced the invasion rate when compared to non-treated cells (70.3 ± 92.5 vs. 1925.7 ± 2077.6 cel
There is a loss of IDO expression and consequently loss of AHR and GCN2 activation during T24 cell invasion. The induction of IDO
gamma diminished T24 cells invasiveness. These results point to a new mechanism of IDO in the bladder tumorigenesis, reinfor
therapeutic target in bladder cancer.

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