# SOTTOMISSIONE ABSTRACT PER RIUNIONE ANNUALE A.I.S.F. 2017

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## Dati dell'abstract

**Categoria**: AUTOIMMUNE & BILIARY DISEASES
**Titolo**: Metformin reduces cell migration and down-regulates epithelial to mesenchymal transition (EMT) by AMPK / Foxo3a pathway in human intrahepatic cholangiocarcinoma (CCA)
**Autori**:

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**TESTO DELL'ABSTRACT**

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CCA is an aggressive cancer resistance to chemotherapeutics. We demonstrated that CCA is enriched of cancer stem cells expressing EMT traits associated with aggressiveness and drug resistance. We established primary cell cultures from human IHCCA subtypes (mucin and mixed). Treatment with the anti-diabetic drug metformin has been associated with reduced cancer incidence. In immortalized cancer cell lines, metformin showed EMT inhibitory effects by up-regulating Foxo3a signaling.
We aimed evaluating the effects of metformin on proliferation,apoptosis, cell migration and expression of EMT traits in primary cultures of CCA subtypes.
CCA were treated with acute increasing metformin concentrations (5-1000μM, 1-4 days) and chronically at 10μM Metformin.

We evaluated proliferation by MTS assay; apoptosis by FlowCytometry analysis of Annexin V-FITC/Propidium Iodide; and cell migration by wound-healing assay. The expression of Vimentin,E-Cadherin,SNAIL1/2,TWIST1,Cytokeratin19,FOXO3a and AMPK genes were analyzed by RT-qPCR, whereas FOXO3a,Cytokeratin19 and Vimentin were analyzed by Immunofluorescence Assay.
Metformin significantly inhibited cell proliferation and induced apoptosis in primary cultures of mucin- and mixed-IHCCA; the effects were dose- and time-dependent. The migration of IHCCA cells, from both mucin and mixed CCA subtypes,was also significantly reduced by acute treatment. The effects of metformin were associated with enhanced gene expression of the epithelial marker E-Cadherin and decreased expression of Vimentin and EMT specific genes, SNAIL1/2 and TWIST1. Metformin also increased the AMPK and FOXO3a mRNA levels.
FOXO3a gene expression was negatively correlated with the expression of SNAIL1 and Vimentin genes.
The FOXO3a protein migrates from cytoplasm to nucleus in metformin treated cells. After chronic treatments the Mucin-IHCCA showed a high expression of Cytocheratin19 and a very low expression of Vimentin.
In conclusion, we demonstrated that metformin inhibits cell proliferation, enhances apoptosis and impairs EMT traits by activating Foxo3a in primary cultures of human CCA. Therefore, metformin could play anticancer effects against human CCAs with relevant therapeutic implications.

☒ Oral ☐Poster

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