AISP - 36th National Congress. **Bologna, Italy. October 4-6, 2012**

The Inflammatory Molecules S100A8 and TGF-b1 Activate the Epithelial-Mesenchymal Transition Process in Pancreatic Cancer Cells

Dania Bozzato, Francesca Simonato, Stefania Moz, Matteo Fassan, Paola Fogar, Andrea Padoan, Ambrogio Fassina, Sergio Pedrazzoli, Mario Plebani, Daniela Basso

Department of Medicine, University of Padua. Padua, Italy

Context Chronic inflammation is suggested to play a key role in cancer initiation and progression. Epithelial-mesenchymal transition (EMT) is an essential developmental program that becomes reactivated in adult tissues to promote the progression of cancer. EMT is characterized by an enhanced cell motility, the loss of the epithelial marker E-cadherin (CDH1), and the overexpression of the mesenchimal marker N-cadherin (CDH2). Master regulators of EMT are the transcription factors Snail, Slug, ZEB and Twist. **Objective** To ascertain whether the inflammatory molecules S100A8, S100A9 and TGF-b1, overexpressed in pancreatic cancer (PaCa), might start the EMT program. **Methods** BxPC3 cells were treated with 10 nM S100A8 or S100A9, 0.02 ng/mL TGF-b1 or with vehicle alone (reference) for 72 hours. The expression (mRNA) of Snail, Slug, ZEB1, ZEB2, Twist, CDH1 and CDH2 were quantified by RT-PCR (Light Cycler). N-cadherin protein expression was evaluated by immunohistochemistry (IHC). **Results** TGF-b1 significantly enhanced the expression of all the tested EMT markers (P=0.037 for CDH1, CDH2, Slug, ZEB1 and ZEB2; P=0.005 for Snail and Twist). S100A8 significantly enhanced the expression levels of Twist (median fold increase: 4, range: 2.6-22.3; P=0.007) while S100A9 did not (median: 2, range: 0.8-9.3, P=0.10). Both molecules reverted TGF-b1 effects on Twist expression (TGF-b1: median: 6, range: 3.6-42.6; TGF-b1 and S100A8: median: 3, range: 2.3-3.8; TGF-b1 and S100A9: median: 3.3, range: 3.1-4.2). By IHC, control cells showed an inhomogeneous non-continuous membranous N-cadherin immunostain. The treatments with both TGF-b1 and S100A8 resulted in an enforced moderate complete membranous immunostain. The combined treatment with TGF-b1 and S100A8 was less effective on protein visualization in comparison to any single treatments (weak to moderate complete immunostain). **Conclusion** TGF-b1 activate the transcriptional program which underlies the EMT in PaCa cells. A dual role for S100A8 in the EMT was shown: it promotes the EMT by inducing Twist mRNA and N-cadherin protein expression, but it antagonizes TGF-b1 effects on both targets. S100A9 exerts only inhibitory effects on TGF-b1.