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S100A8 and S100A9 Target Akt, mTOR and NF-kB Signalling in Pancreatic Cancer Cells

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Context S100A8/S100A9 inflammatory proteins are suggested to be involved in pancreatic cancer (PaCa) progression. S100A8/A9 expression in the neoplastic pancreas correlate with SMAD4 mutational status suggesting possible interactions with TGF-b1. **Objective** To ascertain whether S100A8/S100A9 differently affect Akt, mTOR and NF-kB signalling in PaCa cells with different aggressiveness and whether these molecules interact with TGF-b1. **Methods** Western blotting analyses were used to assess the effects of S100A8, S100A9 and S100A8/A9 on Akt (Ser473, Thr308), mTOR (Ser2448) and NF-kB (p-IkB-a) in BxPC3, Capan1 and MiaPaCa2 PaCa cells lines. S100A8, S100A9, S100A8/A9 were incubated with equimolar concentrations of calcium and TGF-b1 for 24 h at 37°C. Following MALDI-TOF-MS analyses were performed. **Results** In BxPC3 Akt Thr308 was phosphorylated by S100A8/A9, while in Capan1 and MiaPaCa2 S100A8/A9, S100A8 and S100A9 phosphorylated both Akt sites. In Capan1 and MiaPaCa2, not in BxPC3, S100A8, S100A9 and S100A8/A9 caused significant Ser2448 phosphorylation. S6RP, downstream effector of mTORC1, was phosphorylated (Ser235/236) only in S100A8 treated MiaPaCa2. A strong NF-kB activation was induced by S100A8 in BxPC3, by S100A9 and S100A8/A9 in Capan1. NF-kB was inhibited by S100A8 and S100A8/A9, while it was activated by S100A9 in MiaPaCa2. In the presence of TGF-b1 S100A8/A9 effects on Akt Thr308 and Ser473 phosphorylation were significantly modified, suggesting the existence of interactions between TGF-b1 and S100A8/A9. In the presence of calcium ions S100A8 and S100A9 formed, as expected, homo- (21663 m/z and 28346 m/z) and hetero- (25153 m/z) dimers (MALDI-TOF-MS). An absolute new finding was the identification of hetero-complexes formed by S100A9 and TGF-b1 (39803 m/z). **Conclusion** S100A8/A9 proteins in pancreatic cancer might favour cancer cell growth by inducing Akt, mTOR and NF-kB. In the less invasive BxPC3 cells S100A8 activates NF-kB. In more aggressive Capan1 and MiaPaCa2 cells S100A8, S100A9 and S100A8/A9 activate mainly Akt and mTORC1, not NF-kB pathways. TGF-b1 was demonstrated to be a new binding partner of S100A9 and this will open new fields of investigation on these interesting and complex inflammatory proteins in the PaCa setting.