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The Inflammatory Calcium Binding Protein S100A8 and Its N-Terminal Proteolytic Fragment Interact with Transforming Growth Factor-Beta1 (TGF-β1) and Alter Akt, mTOR and NF-kappa B Cancer Cell Signalling

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Context S100A8 is highly expressed by stromal cells in pancreatic cancer when SMAD4 is not mutated or by cancer cells when SMAD4 is mutated, suggesting a link between TGF-β1 and S100A8 pathways. The proteolytic fragment of S100A8, NT-S100A8, highly abundant in pancreatic cancer, is involved in altering insulin secretion and action. **Objective** To ascertain whether S100A8 and NT-S100A8 interacts with TGF-β1 in altering intracellular calcium, NF-kappa B, Akt and mTOR signalling. **Methods** BxPC3 cells were stimulated with S100A8 (10 nM), NT-S100A8 (50 nM) alone or combined with TGF-β1 (0.02 ng/mL). Intracellular calcium was monitored by Fluo4 (epifluroescence). Akt (Ser473,Thr308), mTOR (Ser2448), NF-kappa B (p-IkB-a) were WB analyzed. **Results** NT-S100A8 evoked a train of intracellular calcium fluxes after 150-second lag time, which was reduced to few seconds in the presence of TGF-β1. S100A8 or TGF-β1 alone did not alter intracellular calcium. NF-kappa B signalling was activated in a calcium-dependent manner by S100A8 and by NT-S100A8 in the presence of TGF-β1. Akt Ser473 phosphorylation was reduced by NT-S100A8, TGF-β1 but mainly by their combination. AktThr308 was not affected by the studied molecules. mTOR phosphorylation (Ser2448) was induced by S100A8 and, at a lesser degree, by TGF-β1 and NT-S100A8. The phosphorylation (Ser235/236) of the downstream effector of mTORC1, S6RB, was reduced by TGF-β1 and NT-S100A8 independently, not by S100A8. **Conclusion** NT-S100A8 mimics TGF-β1 inhibitory effects on Akt and mTOR signalling. These two molecules co-operate in inhibiting Akt probably by altering intracellular calcium, while they co-operate in activating NF-kappa B in a calcium-independent manner mimicking the entire S100A8 molecule effect.