Inga Bauer, Alessia Grozio, Denise Lasiglie', Giovanna Basile, Laura Sturla, Mirko Magnone, Giovanna Sociali, Debora Soncini, Irene Caffa, Alessandro Poggi, Gabriele Zoppoli, Michele Cea, Georg Feldmann, Raul Mostoslavsky, Alberto Ballestrero, Franco Patrone, Santina Bruzzone, and Alessio Nencioni (2012). The NAD+-dependent histone deacetylase SIRT6 promotes cytokine production and migration in pancreatic cancer cells by regulating Ca2+ responses. *J. Biol. Chem.* 287 (49), 40924-40937.

Cytokine secretion by cancer cells contributes to cancer-induced symptoms and angiogenesis. Studies show that the sirtuin SIRT6 promotes inflammation by enhancing TNF expression. Here, we aimed to determine whether SIRT6 is involved in conferring an inflammatory phenotype to cancer cells and to define the mechanisms linking SIRT6 to inflammation. We show that SIRT6 enhances the expression of pro-inflammatory cyto/chemokines, such as IL8 and TNF, and promotes cell migration in pancreatic cancer cells by enhancing Ca2+ responses. Via its enzymatic activity, SIRT6 increases the intracellular levels of ADP-ribose, an activator of the Ca2+-channel TRPM2. In turn, TRPM2 and Ca2+ are shown to be involved in SIRT6-induced TNF and IL8 expression. SIRT6 increases the nuclear levels of the Ca2+-dependent transcription factor NFAT and cyclosporin A, a calcineurin inhibitor that reduces NFAT activity, reduces TNF and IL8 expression in SIRT6 overexpressing cells. These results implicate a role for SIRT6 in the synthesis of Ca2+-mobilizing second messengers, in the regulation of Ca2+-dependent transcription factors, and in the expression of pro-inflammatory, pro-angiogenic and chemotactic cytokines. SIRT6 inhibition may help combat cancer-induced inflammation, angiogenesis and metastasis.