Pancreatic ductal adenocarcinoma (PDAC) accounts for the majority of pancreatic cancer (PaCa) cases and is currently incurable with poor prognosis/survival rates (4%-5-year survival). The extensive local tumor invasion, early metastasis/systemic dissemination and resistance to existing cancer therapies are the major characteristics of PaCa and the impediment to effective cure of this disease. Although PaCa has a well-defined spectrum of highly oncogenic lesions (e.g., mutations in K-RAS, p53, p16\(^{ink4a}\), and SMAD4/DPC4), effective therapies have not yet been developed. Therefore, novel molecular targets-based therapeutic strategies are urgently needed. Recently, we discovered that eukaryotic elongation factor-2 kinase (eEF-2K) is dramatically up-regulated in different PaCa cells, promoting their survival, and that targeted-silencing of eEF-2K led to significant cell death (Ashour et al., 2013). However, the role of eEF-2K in the pathways regulating invasion/metastasis and drug-resistance remains largely unknown. Here, we show that siRNA-mediated knockdown of eEF-2K markedly inhibits the invasion of PANC-1 and MIAPaCa-2 cells. Furthermore, rottlerin, which we found to down-regulate eEF-2K expression, also significantly reduced the invasion of both cell lines. We later investigated the involvement of tissue transglutaminase (TG2), a multifunctional enzyme implicated in regulation of cell survival, migration and invasion. We found that eEF-2K regulates TG2 at the transcription level, as evidenced by eEF-2K knockdown-mediated down-regulation of TG2 protein and mRNA levels by Western blot and RT-PCR, respectively. Importantly, siRNA-mediated knock-down of eEF-2K or TG2 separately, suppresses the downstream key cellular pathways supporting PaCa invasion, and recapitulates rottlerin-induced invasion inhibition and correlated events. We also found that inhibition of eEF-2K/TG2 axis suppresses the epithelial-mesenchymal transition (EMT) through the modulation of ZEB1 zinc finger transcription factors, and tight junction proteins, claudins. Moreover, eEF-2K overexpression, by lentivirus-based expression system, led to increased TG2 expression, with concomitant induction in the invasion capability of PaCa cells. eEF-2K overexpression also rescued the cells from rottlerin-induced suppression of invasion and invasion-supporting machineries, suggesting that eEF-2K is a prominent target of rottlerin, and is a central regulator of PaCa cell invasion. We are currently treating PANC-1 tumor xenografts in nude mice with eEF-2K siRNA-nanoparticles to demonstrate the role of eEF-2K in invasion and tumor progression, in order to establish eEF-2K as a potential novel therapeutic target in PaCa. Collectively, our data suggest, for the first time, the pivotal role of eEF-2K in PaCa invasion/progression and possibly tumor growth.