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Tetrandrine inhibits deregulated cell cycle in pancreatic cancer cells: Differential regulation of $p21^{Cip1/Waf1}$, $p27^{Kip1}$ and cyclin D1

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Abstract

Current therapies in Pancreatic Cancer (PaCa) are ineffective due to deregulated cell cycle driven by landscape mutations. In this study, we show for the first time that tetrandrine (TET) inhibits proliferation of the PaCa cells and inhibits PaCa tumor growth. TET inhibits cell cycle transition at G1/S boundary. TET increased levels of $p21^{Cip1/Waf1}$ and $p27^{Kip1}$, had no effect on the levels of CDK4/6 proteins and decreased the levels of cyclin D1 and pRb proteins. TET resulted in changes in mRNA levels of cyclin D1 and $p21^{Cip1/Waf1}$ but had no effect on the mRNA of $p27^{Kip1}$. We show, for the first time in any system, that TET treatment downregulated Skp2, E3 ligase specific for degradation of $p27^{Kip1}$ during the cell cycle. Taken together our results show, that TET indirectly impairs the activities of CDK4/6 to halt deregulated cell cycle and inhibit PaCa tumor growth. These results suggest that TET may serve, as a novel agent for treatment of PaCa, for which there is no effective cure to date.