# Death-Associated Protein Kinase Regulates Vascular Smooth Muscle Cell Signaling and Migration

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## Abstract:

Cardiovascular disease is the number one cause of death for Americans. New treatments are needed for serious conditions like atherosclerosis, as it can lead to stroke and heart attack. Many types of cells contribute to the progression of cardiovascular disease, including smooth muscle cells that comprise the middle layers of arteries. Inappropriate growth and migration of smooth muscle cells into the lumen of arteries has been implicated in vascular diseases. Death associated protein kinase (DAPK) is a protein that has been found to regulate the survival and migration of cancer cells, but has not been well characterized in vascular cells. The objective of this work was to determine the signaling pathways that DAPK regulates in smooth muscle cells. These studies have focused on smooth muscle cells isolated from human coronary arteries (HCASM cells). We have determined that HCASM cells depleted of DAPK exhibit more

rapid migration, showing that DAPK negatively regulates migration of vascular cells. Results from a focused RT-PCR array identified matrix metalloproteinase 9 (MMP9) as a gene that is increased in cells depleted of DAPK. MMP9 is an important enzyme that degrades collagen, a component of the extracellular matrix through which smooth muscle cells migrate during atherosclerosis. We found that DAPK regulates phosphorylation of the NF-kappa B transcription factor p65 at serine 536, a modification previously found to correlate with increased nuclear levels and activity of p65. In DAPK-depleted HCASM cells, there was more phosphorylation of p65, which causes increased MMP9 promoter activity. Additional experiments were conducted using transgenic mice in which the DAPK gene has been deleted. By studying these mice, we have determined that under some circumstances DAPK augments maximal MMP9 levels in mouse carotid arteries which have been injured by ligation surgery via other signaling pathways. MMP9 has been previously implicated as a protein that promotes vascular diseases such as atherosclerosis. Our research in identifying DAPK as a regulator of MMP9 expression identifies a new target for treatment of vascular diseases like atherosclerosis.

## Description:

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