Fatty acids modulate transforming growth factor-beta activity and plasma clearance

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摘要.

Abstract

The activity and plasma clearance of transforming growth factor (TGF)-beta are known to be regulated by activated alpha2-macroglobulin (alpha2M*). This has been implicated in pathophysiological processes, but no small molecule compounds have been reported to modulate TGF-beta activity by affecting the interaction of TGF-beta and alpha2M*. Here, we demonstrate that fatty acids are capable of inhibiting complex formation of TGF-beta isoforms and alpha2M* as demonstrated by nondenaturing and sodium dodecyl sulfate-polyacrylamide gel electrophoresis. This is dependent on carbon chain length (C20, C18, C16, C14 > C12 > C10), degree of unsaturation (polyunsaturated > saturated), and TGF-beta isoforms (TGF-beta1 > TGF-beta2 > TGF-beta3). Arachidonic acid, which is one of the most potent inhibitors, is also capable of dissociating TGF-beta-alpha2M* complexes, but higher concentrations are required. Arachidonic acid appears to inhibit TGF-beta-alpha2M* complex formation by binding specifically to alpha2M* as demonstrated by gel filtration chromatography. Arachidonic acid reverses the inhibitory effect of alpha2M* on TGF-beta binding, TGF-beta-induced growth inhibition, and TGF-beta-induced transcriptional activation in mink lung epithelial cells and affects plasma clearance of TGF-beta-alpha2M* complexes in mice. These results show that fatty acids are effective modulators of TGF-beta activity and plasma clearance and may be useful in treating human diseases through their effects on the interaction of TGF-beta and alpha2M*.