# Engineered microparticles bearing the morphogen Sonic Hedgehog protect endothelial cells against actinomycin D-induced apoptosis



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| Résumé en anglais | It has been reported that microparticles generated from T lymphocytes undergoing activation and apoptosis, bear the morphogen Sonic Hedgehog (MPsShh+), and possessed the dual ability to increase NO and reduce ROS productions. Here, we investigated whether MPsShh+ protected human umbical vein endothelial cells (HUVECs) against actinomycin D (ActD)-induced apoptosis. MPsShh+ were obtained by activation of human lymphocyte with phytohemagglutinin and then, by stimulation with phorbol-12 myristate-13 acetate and ActD. HUVECs were grown for 24 h in absence or presence of pro-apoptotic agent, ActD (1 µg/mL), and/or 10 µg protein/mL of MPsShh+. Apoptosis evaluation was based on flow cytometry, TUNEL labelling and cytochrome c release. We showed that MPsShh+ treatment significantly prevented HUVECs apoptosis evoked by ActD. Also, caspases inhibitor z-vad.fmk (50 µM ) reduced cell death either in presence or in absence of MPsShh+, indicating the implication of caspases in ActD-induced apoptosis. To investigate the implication of Shh pathway in this effect, its agonist SAG and its antagonist CUR61414 were tested. SAG reduced apoptosis in a dose-dependent manner; by itself, CUR61414 had no effect on its own but abolished the antiapoptotic effect of MPsShh, revealing a contribution of Shh pathway. In contrast, MPsShh+ were still able to reduce apoptosis in the presence of NO synthase inhibitor, L-NA (100 µM ), or when the PI3-kinase and ERK were inhibited with LY294002 (10 µM ) and U0126 (10 µM ) respectively, showing that these pathways were not associated with protection against apoptosis. Besides, we explored changes in ROS production at different times, by electronic paramagnetic resonance. ROS levels were increased in ActD-treated cells at 2 h and 10 h. This elevation was prevented by MPsShh+ only at 2 h. When sources of ROS, xanthine oxidase, NAD(P)H oxidase and respiratory chain complex I, were inhibited using allopurinol (50 µM ), apocynin (100 µM ) and rotenone (5 µM), respectively, we found that only rotenone reduced ActD-induced apoptosis. Also, the superoxide dismutase (SOD) mimetic, MnTMPyP (100 µM ), reduced ActD-evoked cell death and the protective effect of MPsShh+. These results indicate that, under these experimental conditions, MPsShh+ may act in the early phase of apoptosis at mitochondrial level and behave as a SOD mimetic. These findings provide additional mechanisms by which MPsShh+ exert their vasculoprotective effects, preserving integrity of endothelial monolayer. Supported by ANR-07-PHYSIO-010-01. |
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**Liens**

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