# ANTIATHEROSCLEROTIC PROPERTIES OF EVEROLIMUS: IN VITRO AND IN VIVO STUDIES

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Everolimus (E) is an orally active immunosuppressive and antiproliferative compound derived from rapamycin. We investigated the potential antiatherosclerotic activity of E in different cell culture models and in cholesterol-fed rabbits subjected to perivascular carotid collar manipulation. In rat smooth muscle cell cultures, E inhibited cell growth and [3H]-thymidine incorporation in a concentration-dependent manner (IC50=1.93x10-8 M and 6.47x10-9 M, respectively) by affecting cell cycle progression. In mouse peritoneal macrophages, E (10-10 to 10-6 M) caused a concentration-dependent increase (up to 50%, $p<0.01$) of esterified cholesterol biosynthesis induced by acetylated LDL, and this effect was consequent to a stimulation of the esterifying enzyme ACAT activity (up to 40%, $p<0.05$). Cholesterol efflux induced by HDL was increased up to 50% leading to a 18% reduction of total cellular cholesterol content. Furthermore, everolimus reduced up to 30% triglycerides biosynthesis. In New Zealand White rabbits fed a 1% cholesterol diet for 4 weeks and randomized to everolimus (1.5 mg/kg given 1 day before collaring followed by 1 mg/kg per day for 14 days, administered by oral gavage) or vehicle control (N=14 per group), E reduced the I/M ratio by 32% and decreased macrophage content by 65% ($p<0.05$ vs vehicle). Altogether the present findings highlight the ability of E to interfere with several processes involved in atherogenesis, such as SMC proliferation, cellular cholesterol homeostasis, and macrophage accumulation within the intima.

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