Resveratrol Inhibits Pathologic Retinal Neovascularization in Vldlr−/− Mice

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Abstract

Adult retinal angiogenesis and choroidal angiogenesis are common causes of vision loss.1,2 Macular telangiectasia (MacTel), also known as idiopathic parfoveal telangiectasia, is a retinal neovascular disease in which there is abnormal retinal neovascular proliferation in the perimacular area2,1 associated with photoreceptor degeneration.1,4 The pathogenesis of MacTel is not yet understood, though aging might be a contributing factor because MacTel is typically diagnosed in patients in their 50s or 60s. Regrettably, there is no recognized treatment for MacTel to date. Preclinical studies using animal models that mimic MacTel would significantly help to evaluate novel potential therapeutic strategies.

Similar to MacTel and retinal angiomatous proliferation (RAP),5,6 the very low-density lipoprotein receptor (VLDLR) mutant mouse (Vldlr−/−) shows patchy retinal neovascularization (NV) arising from the deep retinal vascular layer. These changes become visible by the end of the second postnatal week, and by 4 weeks of age the NV lesions extend through the normally avascular photoreceptor layer toward the surface of the retinal pigment epithelium (RPE). NV lesions form subretinal clusters of abnormal microvessels reminiscent of those observed in patients with MacTel.5,6 VegfA (Vegf) is elevated in Vldlr−/− retina and is likely one of the primary causes of the proliferation of subretinal neovascular lesions and their leakiness.6,8 Vldlr−/− mouse retinas also show photoreceptor degeneration and Müller glial activation9 associated with subretinal neovascular lesions, indicating a focal increase of retinal neuronal stress. Importantly, the NV lesions in both MacTel patients and Vldlr−/− mice originate from the retinal vessels without initial RPE damage, in contrast to wet age-related macular degeneration, in which NV grows from the choroid through defects in Bruch’s membrane into the subretinal space.6 Although the molecular mechanisms leading to these vascular and neuronal lesions in Vldlr−/− mice are not fully understood, hypoxia, inflammation,9 and Wnt signaling10 may play a role in NV development. Antioxidants ameliorate both the retinal degeneration and the vascular pathology in Vldlr−/− retinas.6
In this study we evaluated the therapeutic potential of resveratrol, a plant polyphenol, for the treatment of subretinal NV using Vldlr−/− mice as a model for MacTel. Resveratrol is found in grapes, peanuts, pines, and red wines, and its intake has been associated with a reduced risk of cardiovascular disease. In animal models, resveratrol also inhibits angiogenesis in cancer, in development and wound healing through downregulation of the MAPK pathway in endothelial cells, leading to reduced endothelial proliferation and migration. Yet in other conditions such as stroke, myocardial infarction, and ischemia-reperfusion injuries, resveratrol can be proangiogenic while at the same time exerting neuroprotective properties.

Our results show that the oral administration of resveratrol significantly suppresses pathologic NV formation in Vldlr−/− mice when treated after the onset of neovascular lesions but also when started before the lesions fully form. The antiangiogenic and amigulatory effects of resveratrol are seen in an ex vivo aortic ring assay and in cell culture experiments. Additionally, resveratrol treatment significantly reduces Vegf transcription in Vldlr−/− retinas and diminishes VEGF-induced phosphorylation of MAPK in vitro. Together these results suggest resveratrol reduces neovascular lesions in Vldlr−/− retinas through the downregulation of VEGF and an attenuated response of retinal endothelial cells to angiogenic stimulation.

METHODS

Animals and Housing
All studies adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by the Children’s Hospital Boston Animal Care and Use Committee. Breeding pairs of mice with insertion mutation of the Vldlr gene (B6;129S7-Vldlr(1Her)H11002, stock number 002529) and wildtype (WT) mice on the same genetic background were purchased from the Jackson Laboratory (Bar Harbor, ME). The Vldlr(1Her) mutation contains a partial deletion of exon 5 in the Vldlr gene and an inserted neomycin cassette that disrupts the reading frame; therefore, no Vldlr protein is detectable by immunoblot analysis. The homozygous mutant mice are viable and fertile. All animals were housed in a 12-hour light/12-hour dark cycle and given food ad libitum.

Resveratrol Treatment
Mice were treated with resveratrol using two different protocols. For the first one, weaned (P21) Vldlr−/− mice were supplied with a defined rodent diet AIN-93G supplemented with 2.4 g resveratrol/kg solid chow (equals 0.36 g/kg body weight, calculated from 150 g/kg body weight daily food intake of a mouse) or control AIN-93G feed (Research Diets Incorporated, New Brunswick, NJ). Fresh food was provided every week until the end of the experiment at P60. In a second experiment, 1 g/kg body weight of a micronized formulation of resveratrol (1 g micronized resveratrol/kg body weight in 10 μL of 2% HPMC, 0.2% DSS, 1% sucrose in water) or vehicle only as control was given by oral gavage to Vldlr−/− pups daily after postnatal day (P) 10 to P30, before the onset of subretinal neovascularization. Littermate controls were used in all experiments.

Quantification of Retinal Neovascularization
Vldlr−/− and control WT mice were euthanized at P60 (solid Chow fed) or P30 (gavage treated) with lethal doses of tribromoethanol (Avertin; Sigma). Aortas were dissected free from adventitia and cut into 1-mm-thick rings. Individual rings were placed in growth factor-reduced basement membrane matrix (Matrigel; BD Biosciences, Franklin Lakes, NJ) in 24-well tissue culture plates (Costar) in 2% FBS in Eagle’s minimum essential medium and incubated for 4 days in medium (EBM-2; Clonetics, Walkersville, MD) containing growth factor boost but no steroids (CC-4176, Clonetics). Resveratrol (50 μM) or vehicle solution (2% HPMC, 0.2% DSS in water) was added to the indicated wells. Microphotographs of each well were taken after 6 days’ incubation, and images were quantified (Photoshop; Adobe) by measuring the area covered by outgrowth of the aortic ring. Results are expressed as mean ± SEM.

Aortic Ring Assay
Aortic ring assays were carried out as previously described. In brief, adult Vldlr−/− and WT mice were perfused with PBS after a lethal intraperitoneal dose of tribromoethanol (Avertin; Sigma). Aortas were dissected free from adventitia and cut into 1-mm-thick rings. Individual rings were placed in growth factor-reduced basement membrane matrix (Matrigel; BD Biosciences, Franklin Lakes, NJ) in 24-well tissue culture plates and incubated for 4 days in medium (EBM-2; Clonetics, Walkersville, MD) containing growth factor boost but no steroids (CC-4176, Clonetics). Resveratrol (50 μM) or vehicle solution (2% HPMC, 0.2% DSS in water) was added to the indicated wells. Microphotographs of each well were taken after 6 days’ incubation, and images were quantified (Photoshop; Adobe) by measuring the area covered by outgrowth of the aortic ring. Results are expressed as mean ± SEM.

Quantitative Analysis of Gene Expression
RNA samples from whole retina or laser-captured samples were treated with DNase I (Qiagen) and then reverse transcribed (Invitrogen) to cDNA for quantitative real-time PCR (qRT-PCR). PCR primers targeting murine Vegf and Gfap and an internal control gene, cyclophilin, were designed using NCBI Primer Blast with sequences that specifically detect all known isoforms of the target genes. Gene expression was quantified with a sequence detection system (7700 TaqMan; ABI Prism) and the SYBR Green master mix kit. Data were analyzed using the ΔΔCt method.

Immunofluorescence of Cryosections
Eyes from Vldlr−/− and WT mice at P15, P30, and P60 were collected and fixed in 4% PFA for 1 hour at 4°C. The cornea and lens were removed, and the eyeball was immersed in 30% sucrose for 2 hours, embedded in optimum cutting temperature (OCT) medium, and stored at −80°C until processed. Eight-micrometer sections were cut and incubated with primary anti-GFAP antibody (1:1000, Abcam) for 1 hour. After a wash and incubation in the secondary antibody, sections were embedded in reagent (SlowFade Antifade; Invitrogen) with DAPI for microscopy.
Boyd Chamber Cell Migration Assay

Human renal microvascular endothelial cells (HRMECs; Cell Systems) at approximately 70% confluence were serum starved overnight and seeded on Boyd Chambers (25,000 cells/well). Cells were incubated in basal media with 0.5% FBS and 20 ng/mL VEGF or bFGF and 50 μM resveratrol or vehicle. After 4 hours at 37°C and 5% CO2, the cells were fixed in 4% PFA and stained with DAPI. The cleaned membrane was embedded for microscopy, and migrated cells were quantified.

HRMEC Culture and Conditional Stimulation

HRMECs were cultured in six-well plates until they were approximately 70% confluent, then they were serum starved overnight. The cells were incubated for 4 hours with resveratrol or vehicle at 37°C and 5% CO2. Thirty minutes, washed twice in 4°C PBS, and lysed in RIPA buffer with phosphatase and protease inhibitors (Sigma). Samples were centrifuged at 4°C, and supernatant protein samples were collected for Western blots.

Western Blot Analysis

Protein extracts of lysates from HRMEC cultures or from homogenized retinas of Vldlr−/− mice were used in Western blots. Total protein concentration was measured using a BCA assay (Pierce, Rockford, IL). Fifty micrograms of each protein sample was loaded on an SDS-PAGE gel for electrophoresis. The gel was blotted onto a polyvinylidene difluoride membrane. The primary antibodies were rabbit monoclonal against total ERK1/2, p42/44 phosphorylated ERK1/2 (4695 and 43965, respectively; Cell Signaling Technology, Danvers, MA), and rabbit polyclonal anti-Fgf2 (R&D Systems). The primary antibody was applied overnight in 5% BSA at 4°C. Membranes were then incubated with horseradish peroxidase-conjugated goat antibody to rabbit IgG (1:1000, Amersham) and developed on Kodak film. Antibodies were used according to manufacturer’s recommendations. Samples from three independent experiments for each condition were used in the Western blot. Densitometry was analyzed using ImageJ software (developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index.html).

Statistical Analysis

All values are expressed as mean ± SEM. Comparison between two groups was analyzed using Student’s t-test. Comparison between more than two groups was performed using ANOVA with Tukey-Kramer HSD correcting for multiple testing. Differences between experimental groups were considered statistically significant or highly significant at values of P ≤ 0.05 or P ≤ 0.01, respectively.

Results

Characterization of Retinal Neovascularization in Vldlr−/− Mice

NV in Vldlr−/− mice is first detectable in the outer nuclear layer (ONL) at P15 and is associated with Müller cell activation and local neuronal cell death.6 We confirmed these characteristic findings in Vldlr−/− retinas with deep penetrating retinal vessels originating from the vasculature in the outer plexiform layer (OPL) of the retina, growing through the normally avascular ONL into the subretinal space at P15 (Fig. 1A). We also confirmed focal activation of Müller cells in the Vldlr−/− retinas associated with the sites of vascular lesion (Fig. 1B). In addition, 3D reconstruction of the neovascular lesions in P30 Vldlr−/− mice demonstrates that the abnormal vessels in the ONL are connected to the deep layer of the retinal capillary network in the OPL and extend downward to form abnormal neovascular clusters on the surface of the RPE, demonstrating the retinal origin of these subretinal vascular clusters (Figs. 1C, 1D).

Inhibition of Retinal Neovascularization in Vldlr−/− Mice Treated with Resveratrol

To evaluate the potential therapeutic effect of resveratrol after the onset of subretinal NV, Vldlr−/− mice and littermate controls were fed with regular or resveratrol-supplemented (0.36 g/kg/d) solid chow from P21 through P60. Retinas from Vldlr−/− mice treated with resveratrol showed significantly fewer subretinal NV lesions at P60 (102.1 ± 4.9 lesions per

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Pathologic subretinal neovascularization in Vldlr−/− mouse retina. (A) Cross-section of Vldlr−/− retina at P15. Endothelial cells stained with isolectin B4 (red) at the early stage of abnormal growth of deeper penetrating vessels (white arrows) extending from the OPL, where the deep layer of retinal capillary networks normally stop, across the ONL toward the photoreceptor outer segments and RPE. Gfap was present (green) in the astrocytes around the superficial layer of vessels only. (B) At P30, multiple foci of positive GFAP staining (green) were present in Müller cells spanning the retinal layers (white arrows). (C, D) 3D reconstruction of isolectin B4 stained neovascularization between the OPL and RPE layers at P30, culminating in a subretinal neovascular mass on the surface of the photoreceptor side of the RPE (white arrows).
retina; \( n = 18 \) compared with controls (166.7 ± 11.9 lesions per retina; \( n = 15 \); \( P < 0.00001 \); Fig. 2A). To investigate whether resveratrol also prevents the early stages of NV formation, we treated \( Vldlr^{-/-} \) mice from P10 to P30 with resveratrol (1 g/kg/d by oral gavage). In this approach, resveratrol treatment coincides with the onset of NV formation (P15). We found that resveratrol reduced the number of subretinal NV lesions (22.6 ± 5.4 vs. 70.9 ± 10.2 lesions per retina; \( n = 10 \); \( P = 0.0001 \); Fig. 2B).

**Resveratrol Inhibits Vascular Sprouting Ex Vivo**

To confirm the antiangiogenic effect of resveratrol in vitro, we used aortic explants isolated from WT and \( Vldlr^{-/-} \) mice. Resveratrol treatment reduced the area of endothelial cell sprouting in both WT and \( Vldlr^{-/-} \) aortas (WT, 9.7 ± 0.6 mm\(^2\) vs. 21.8 ± 0.1 mm\(^2\), \( n = 6 \) per group, \( P = 3.7 \times 10^{-8} \); \( Vldlr^{-/-} \), 13.0 ± 1.0 mm\(^2\) vs. 24.3 ± 2.3 mm\(^2\), \( n = 6 \) per group, \( P < 0.002 \); Fig. 2C). This suggests that the antiangiogenic effect of resveratrol is not dependent on the \( Vldlr \) mutation.

**Neovascular Lesions in the \( Vldlr^{-/-} \) Retina Show Focal Upregulation of Vegf and Gfap**

Previous studies have shown an upregulation of \( Vegf \) and \( Gfap \) in the whole retina of \( Vldlr^{-/-} \) mice compared with WT controls.\(^6,8\) To quantify \( Vegf \) and \( Gfap \) gene expression specifically in the lesions, we used laser capture microdissection to isolate individual retinal layers in lesion areas and in nonlesion areas in \( Vldlr^{-/-} \) retinas and in the corresponding layers of WT control retinas. Four layers were captured in each group: ganglion cell layer (GCL), inner nuclear layer (INL), outer nuclear layer (ONL) and RPE layer (Fig. 3A). We used quantitative RT-PCR on each laser captured retinal layer to assess the mRNA expression of \( Vegf \) and \( Gfap \).

We find the highest expression of \( Vegf \) mRNA in ONL and RPE of \( Vldlr^{-/-} \) around the area of the NV lesions. \( Vegf \) mRNA from the \( Vldlr^{-/-} \) ONL lesion area was increased 6.7-fold compared with the ONL of an adjacent nonlesion region in the \( Vldlr^{-/-} \) retina and increased 18.6-fold over ONL in WT reti-
Resveratrol Reduces VEGF and Gfap Expression in Vldlr−/− Retinas

As expected, based on layer-specific analysis, the VEGF mRNA levels in whole retinas from Vldlr−/− mice were significantly higher than in WT retinas (Fig. 3Bi). Interestingly, resveratrol treatment from P21 to P60 in Vldlr−/− mice markedly reduced VEGF mRNA expression to levels found in WT retinas ANOVA (α = 0.0001; n = 3 per group). Gfap mRNA expression in Vldlr−/− retinas was also significantly higher than in WT retinas (Fig. 3Bii), and resveratrol treatment reduced the transcript level close to twofold. These results suggest that resveratrol treatment in Vldlr−/− retinas was associated with a decrease in retinal VEGF expression and a reduction of local glial stress. In addition, Rhodopsin mRNA level in the Vldlr−/− retinas showed a trend toward a decrease compared with WT, indicating that potential rod photoreceptor loss may be associated with the Vldlr−/− phenotype (Fig. 3Biii). Levels of Cone opsin mRNA did not vary significantly between WT and Vldlr−/− retinas, possibly reflecting primary damage to rods but not to cones (Fig. 3Biv).

Resveratrol Inhibits Endothelial Cell Migration and ERK1/2 Phosphorylation

We next examined the effects of resveratrol on downstream signaling. An in vitro migration assay with HRMECs demonstrated that VEGF-stimulated migration of HRMECs is significantly inhibited by resveratrol (147 ± 2 cells/membrane in...
VEGF incubated wells vs. 26 ± 4 cells/membrane with VEGF and resveratrol; P = 6.0 × 10⁻⁵; n = 3 per group; Fig. 4A). This antimigratory effect of resveratrol is not VEGF specific because we observed a similar inhibition of bFGF-induced HRMEC migration (289 ± 12 cells/membrane in bFGF-incubated wells and 88 ± 12 cells/membrane in wells incubated with both bFGF and resveratrol; P = 0.0001; n = 3 per group; Supplementary Fig. S2A, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-6496/-/DCSupplemental). Resveratrol treatment also reduced retinal expression of Fgf2 protein, the murine form of basic FGF (bFGF; Supplementary Fig. S2B, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-6496/-/DCSupplemental), supporting the notion that resveratrol effects are not exclusively limited to antagonizing VEGF.

Given that the ERK1/2 MAPK pathways are important for mediating VEGF-induced endothelial migration and proliferation,²⁵ we evaluated the effect of resveratrol on VEGF-induced ERK1/2 phosphorylation in HRMECs. We found that resveratrol-treated HRMECs have significantly less phosphorylated ERK1/2 than control (22% ± 3% of total ERK1/2 with basal media, 51% ± 5% with VEGF, and 11% ± 7% with VEGF + resveratrol; Student’s t-test between the latter two groups; P < 0.001; n = 3; Figs. 4B, 4C). These findings suggest that the effect of resveratrol on VEGF-induced endothelial migration is likely mediated, at least in part, through a decreased activation state of ERK1/2.

**DISCUSSION**

There is no clinically recognized treatment for MacTel to date. Several recent small-scale studies find that intravitreal injection of bevacizumab reduces vascular leakage in MacTel patients. However, the effects of bevacizumab on photoreceptor cell loss or improvement of visual acuity in MacTel patients are less clear.²⁶–²⁸ Similarly, other small-scale studies on RAP, with retinal NV like MacTel, find that intravitreal injection of VEGF-inhibitors reduce vascular leakage in the short term (up to 22 months).²⁹–³³ However, there are no data for the long-term outcome of these treatments, especially with regard to visual acuity. This is important in light of studies reporting that direct inhibition of VEGF may decrease neuroprotection,³⁴ which might have negative consequences in an already stressed retina. Our study finds that oral treatment with resveratrol reduces NV in Vldlr⁻/⁻ mice and may be a novel potential therapeutic option for MacTel patients.

The Vldlr⁻/⁻ mouse model replicates several critical features of MacTel and RAP, such as NV proliferation originating from retinal vessels with focal leakage and photoreceptor cell death. Increased VEGF expression is suggested by the vascular leakage in MacTel²⁶ and RAP,²⁹ and this notion is supported by the reduction of NV progression with bevacizumab or ranibizumab (Lucentis) injections in these patients. Concordant with these clinical observations, the upregulation of VEGF in Vldlr⁻/⁻ retinas is found in this study and several previous reports.³⁵–³⁷ In addition, our investigation is the first to describe a distinct localized expression pattern of VEGF and Gfap in Vldlr⁻/⁻ retinas. The upregulation of VEGF is found to be most prominent in the ONL of neovascular lesion areas. Gfap mRNA is also found throughout the Vldlr⁻/⁻ eyes, most abundantly within the NV lesion areas; however, unlike VEGF, Gfap is found mainly in the GCL (Fig. 3A). Gial cell activation in this model is consistent with reports that Muller glial cells may be involved in MacTel.³⁵

Importantly, our results provide evidence that oral resveratrol reduces pathologic NV in Vldlr⁻/⁻ mouse retinas when administered either before or after the onset of the formation of NV lesions. Resveratrol may be useful for clinical interventions at different stages of MacTel. We found that the reduction of retinal NV in resveratrol-treated mice is associated with a reduction of retinal VEGF transcription in Vldlr⁻/⁻ retinas. Moreover, resveratrol also reduces the migration and proliferation of endothelial cells toward different angiogenic cues in both Vldlr⁻/⁻ and WT mice in aortic ring explant assays, suggesting that the antiangiogenic effect of resveratrol is not dependent on the Vldlr mutation. This observation is in line with a previous report showing that resveratrol regulates pathologic angiogenesis through a novel sirtuin-independent elongation factor 2 kinase pathway.³⁶ We found that although some inflammation markers, such as TNFa, are upregulated in Vldlr⁻/⁻ retinas compared with wild-type controls, as reported previously,⁹ resveratrol treatment in Vldlr⁻/⁻ retinas does not significantly change the overall inflammation profile of these markers compared with nontreated Vldlr⁻/⁻ retinas (data not shown), suggesting that the protective effects of resveratrol in this model are not caused primarily by alterations of inflammatory pathways. In addition, resveratrol inhibits bFGF-induced endo-

![Figure 4](http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-6496/-/DCSupplemental)

**FIGURE 4.** Reduced HRMEC migration and ERK1/2 phosphorylation with resveratrol treatment. (A) Endothelial cell migration assay in a Boyden chamber. In the presence of VEGF (20 ng/ml), coinubation with resveratrol (50 μM) significantly reduced the migration of HRMEC after 4 hours (Student’s t-test, ***P = 0.0001; n = 3 for each group). (B) Western blot of phosphorylated ERK1/2 and total ERK1/2 in HRMECs. (C) Pretreatment with resveratrol before stimulation with VEGF in HRMEC monolayer culture significantly diminished the p-ERK1/2 to total ERK1/2 ratio, compared with wells without resveratrol. (Student’s t-test, ***P = 0.001; n = 3 for each group).
Vldlr ischemia-reperfusion injuries \(^{15-17}\) and can also act as an anti-to preserve photoreceptors. The effects of resveratrol may not these concentrations inhibits retinal NV formation and is likely

Importantly, based on the trend of rescued \(Rhodopsin\) expression in resveratrol-treated eyes, this compound may also, directly or indirectly, protect against rod photoreceptor degeneration, which agrees with a previous report \(^{16}\) and supports investigation into the potential benefits of resveratrol in treating patients.

Overall, the significant protective effects of resveratrol observed in \(Vldlr^{-/-}\) mice suggest the possibility of using resveratrol as a safe treatment option for MacTel. We used a daily dose of 0.56 or 1.0 g resveratrol/kg body weight, which is considered feasible for humans. \(^{19}\) We found that resveratrol at these concentrations inhibits retinal NV formation and is likely to preserve photoreceptors. The effects of resveratrol may not be limited to the pathways investigated in this study because resveratrol has been found to have cytoprotective properties in ischemic conditions such as stroke, myocardial infarction and ischemia-reperfusion injuries \(^{15-17}\) and can also act as an antioxidant. \(^{37-41}\) In summary, our study provides the first evidence that the oral administration of resveratrol is a potential, safe, and effective intervention for treating patients with MacTel. These findings may be extended to similar neovascular retinal conditions such as RAP.

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References


