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Review

Significance of the antiangiogenic mechanisms of thalidomide in the therapy of diabetic retinopathy

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ABSTRACT

Diabetic retinopathy is an ocular complication associated with the chronic endocrine disorder of diabetes mellitus. Angiogenesis is adjudged as a prime modulatory event in this complication. The formation of new blood vessels on the pre-existing vasculature gives rise to an abundance of anatomical and physiological alterations which ultimately results in vision loss. The drastic consequences of this complication prompt the obligation of developing effective therapies for its cure. The existing therapy mainly includes destructive techniques such as laser photocoagulation. Owing to the various drawbacks associated with this technique, there is a need to develop alternative therapies which could halt the progression of diabetic retinopathy without causing considerable damage to the retinal cells. One such possible alternative treatment being researched upon is the antiangiogenic therapy. Since angiogenesis is a critical event during the progression of this disorder, targeting this event may perhaps prove effective in its treatment. Amongst several antiangiogenic agents, thalidomide holds a reputable position due to its effectiveness in terminating angiogenesis during various pathological conditions. This review focuses on the diverse molecular mechanisms proposed to explain the antiangiogenic properties of thalidomide and their applicability in diabetic retinopathy.

Contents

1. Introduction

Diabetic retinopathy is one of the most complex microvascular complications associated with the metabolic disorder of diabetes mellitus. The hyperglycemic conditions prevalent in the body of a diabetic person are herald of the various molecular damages which gradually induce irreversible injury to the vasculature of the body in various parts, resulting in different diabetic complications. These complications are named after the specific regions whose blood vessels get affected by the hyperglycemia-induced molecular damage. For example, if the damage to the vasculature is confined to the blood vessels of retinal region, the condition is concretely termed as diabetic retinopathy. Other

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such complications of diabetes mellitus include — damage to the blood vessels of glomeruli (diabetic nephropathy) and irreversible injury to the blood vessels supplying nutrients to the nerve cells (diabetic neuropathy). All the complications associated with diabetes mellitus are more nocuous and deleterious than the disorder of diabetes itself. Diabetic retinopathy is associated with severe damage to the retinal blood vessels, which eventually lead to numerous changes in the anatomical structure and basic physiology of the eyes, ultimately resulting in blindness [1,2]. Till date, the most effective therapy developed for treating diabetic retinopathy is laser photocoagulation. This technique primarily focuses on coagulating the proteins of a small area of the retinal cells. This is done by providing light energy (in the form of laser), which later converts into thermal energy after getting absorbed by the retinal cells. The coagulation of proteins in the targeted cells results in their destruction. This destruction of the retinal cells in a small area acts as a protection barrier in two ways. First, it causes coagulation of blood in the treated area, which can be exploited as a seal for the blood vessels and hence ceases any further vascular leakage or hemorrhage in the vitreous chamber. Second, it blocks any further molecular damage to the neighboring epithelial cells of the treated region. However, since this technique is destructive in nature, it accompanies quite a lot of drawbacks which include — severely reduced night vision, loss of peripheral vision, blind spots in the central vision, increased sensitivity of the eyes towards light and other vision-related complications. Besides, it has some other limitations such as not being able to restrict retinopathy even after complete laser therapy and its inability to restore the vision already lost in the course of the disorder [3,4]. Another therapeutic method, namely vitreoretinal surgery, has been developed but it also presents with its own injunctions. It is quite expensive and a complicated procedure, besides, requiring the involvement of a specialist practitioner for performing such surgery. Hence, owing to the constraints of the existing therapies, there is a need to develop advanced alternative treatments for curing diabetic retinopathy. The most worked-upon area in this field of research is the development of anti-angiogenic agents. Since angiogenesis is one of the detrimental events in the progression of diabetic retinopathy, targeting it would probably help in halting the development of abnormally growing blood vessels in the retinal region. The consequence of this blockage would be a reduction in the progression of diabetic retinopathy [5]. One such agent being researched upon, for its antiangiogenic properties, is thalidomide. Thalidomide has been proven to inhibit the process of angiogenesis in several tumor progressions. This led to the speculation that it might also be utilized for inducing similar inhibition in diabetic retinopathy. Several studies done till now in this regard have given positive results. Further studies are being carried out to validate its efficacy in preventing the progression of diabetic retinopathy. (See Figs. 1– 4.) (See Tables 1 and 2.)

2. Diabetic retinopathy

Diabetic retinopathy is a severe sight-threatening complication associated with diabetes mellitus. It is one of the most common causes of preventable blindness in the world. The risk of developing microvascular diabetic complications increases in diabetic patients with an increase in the duration of time for which they had been suffering with diabetes. This statement is supported by evidential statistical data regarding the occurrence of diabetic retinopathy. This data concludes that the chances of development of diabetic retinopathy in the patients

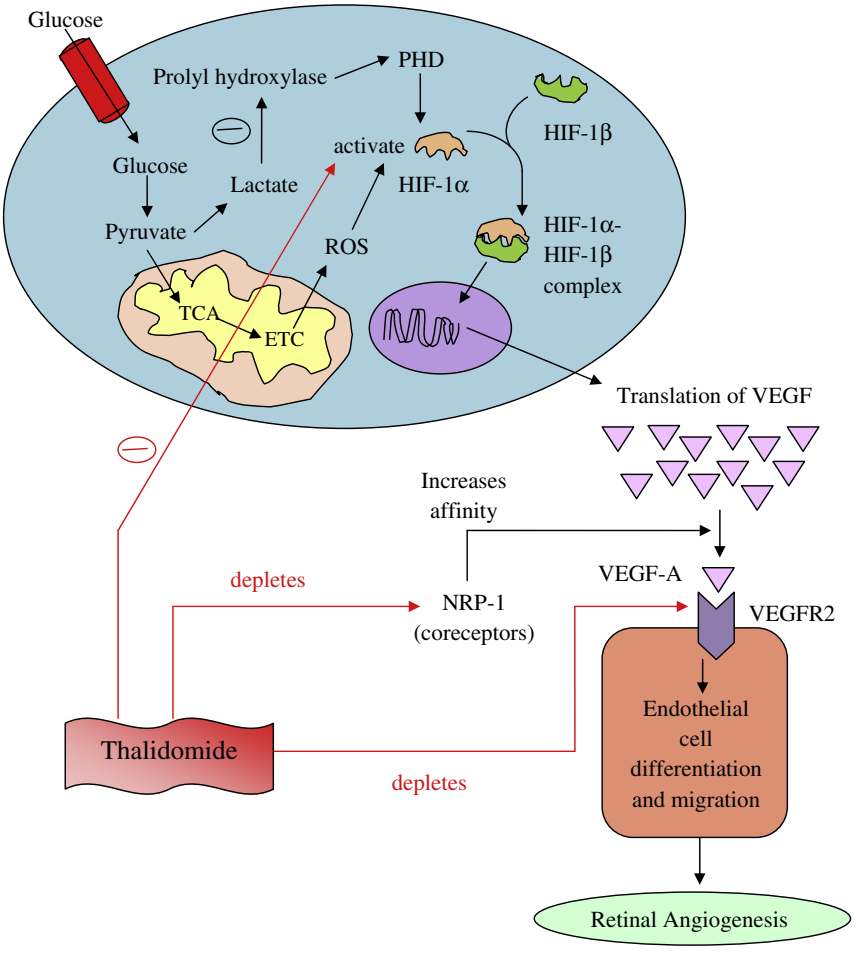

Fig. 1. Inhibition of HIF-1 activation and depletion of VEGF receptors by thalidomide results in downregulation of retinal angiogenesis.

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