

## Chemerin - A Damage Factor that Promotes the Progression of Diabetic Retinopathy

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### ABSTRACT

Diabetic retinopathy is a serious eye disease that leads to blindness, and its development is related to inflammation, oxidative damage, and various pro-angiogenic cytokines. Studies in recent years have found that chemerin plays an important role in the development of DR. And the chemerin is also involved in the formation of retinal neovascularization. Therefore, in this article, we expound the relationship between chemerin and DR and its role in the formation of RNV.

**Keywords:** Diabetic retinopathy, Retinal neovascularization, Chemerin

**Abbreviations:** DR: Diabetic Retinopathy; RNV: Retinal Neovascularization; PDR: Proliferative Diabetic Retinopathy; cAMP: Cyclic Adenosine Monophosphate; FFA: Free Fatty acids; MAPK: Mitogen-Activated Protein Kinase; CRP: C-Reactive Protein; PI3K: Phosphatidyl Inositol 3 Kinase; MMP: Matrix Metalloproteinase

### INTRODUCTION

Diabetic retinopathy (DR), a serious ocular complication caused by diabetes, is an important cause of blindness in the working population. The development of DR is closely related to oxidative damage, inflammation and various pro-angiogenic cytokines [1]. The formation of retinal neovascularization (RNV) is the main pathological change of proliferative diabetic retinopathy (PDR). In recent years, studies have found that Chemerin plays an important role in the development of DR [2,3]. Chemerin can play an important biological role in the body by binding to its receptors. First, Chemerin can inhibit the synthesis of cyclic adenosine monophosphate (cAMP), activate hormone-sensitive lipase, promote the metabolism of fat cells, and release glycerol and free fatty acids (FFA) [4]. Chemerin was found to increase the level of human preadipocytes and 3T3-L1 cells in the process of adipocyte differentiation [5,6].

### CHEMERIN PROMOTES INFLAMMATION

The study found that chemerin can promote the migration and recruitment of dendritic cells and macrophages [7], participate in tissue immune and inflammatory responses. Chemerin is generally generated in the early stage of inflammation [8]. Chemerin binding to its receptor CMKLR1 can activate the nuclear factor- $\kappa$ B and mitogen-

activated protein kinase (MAPK) pathways in monocytes, macrophages and immature dendritic cells [9], which play a role in the inflammatory response. Other studies have also confirmed that chemerin is closely related to inflammatory markers, such as TNF- $\alpha$  and Il-6 [10,11]. Serum chemerin level is positively correlated with C-reactive protein (CRP) [12,13] that is a marker of inflammation. In addition, the expression of CMKLR1 in vascular endothelial cells was regulated by inflammatory cytokines [14]. These results suggest that chemerin and its receptor CMKLR1 system may play a role in the inflammatory state of vascular endothelial cells.

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## CHEMERIN IS INVOLVED IN OXIDATIVE STRESS

In human vascular endothelial cells, chemerin can increase the production of mitochondrial ROS [15]. The increase of ROS can increase the level of oxidative stress, thus aggravating oxidative damage. The generation of chemerin-related ROS can be reduced by using shRNA to knock out chemerin receptors or by using anti-oxidative therapy targeting mitochondria [15]. Another study found that chemerin is closely related to 8-isoprostaglandin F<sub>2</sub> (8-iso-pgf<sub>2</sub>), which is an indicator of oxidative stress process [16]. Chemerin can improve oxidative stress response [9] and is negatively correlated with HDL-linked paraoxonase-1 enzyme in the body. Thus, chemerin plays an important role in oxidative stress [17].

## CHEMERIN PROMOTES NEOVASCULARIZATION

Recent studies have also found that chemerin is involved in the formation of neovascularization [18]. Chemerin and its receptor CMKLR1 system under the condition of the inflammation can promote cell migration [7]. Chemerin can induce the formation of neovascularization in human endothelial cells and promote the endothelial cells migration and tube formation, and activate endothelial cells gelatinases (MMP-2/-9) and phosphatidylinositol 3 kinase (PI3K)/AKT and MAPK pathways, these are the key mechanism of angiogenesis and cell survival [19]. Chemerin can promote angiogenesis through inflammatory pathways. The early stage of inflammatory can stimulate the mobilization and homing of endothelial progenitor cells, proliferate and differentiate into mature endothelial cells, which is helpful to repair the injury induced by the inflammatory and promote the formation of neovascularization [20]. Matrix metalloproteinase-2 (MMP-2) and Matrix metalloproteinases-9 (MMP-9) play an important role in angiogenesis, which can degrade collagen type IV extracellular matrix, prompting the extracellular matrix remodeling and cell migration [21,22]. Chemerin can induce the MMP-2 and MMP-9 and then promote vascular endothelial cell regeneration [19]. Chemerin can promote angiogenesis in a dose-dependent manner [18]. Therefore, chemerin may promote neovascularization in many ways.

In previous studies, it was found that the expression of chemerin was increased in the serum of patients with diabetic retinopathy, especially in the patients with PDR [2]. Some scholars also found that the expression of chemerin in the intraocular fluid of PDR patients was significantly increased [3]. And chemerin plays a key role in angiogenesis *in vitro* [19], it can significantly promote the proliferation, migration and tube formation of retinal endothelial cells [23]. Therefore chemerin may play an important role in the pathogenesis of diabetic retinopathy by promoting inflammatory, oxidative stress and angiogenesis.

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