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Signal transducer and activator of transcription 3 (STAT3) signaling in retinal pigment epithelium cells

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Abbreviations: STAT3, signal transducer and activator of transcription 3; RPE, retinal pigmented epithelium; JAK, Janus kinase; TLR, toll-like receptor; VEGF, vascular endothelial growth factor; AMD, age-related macular degeneration; UVB, medial wave ultraviolet light; CFB, complement factor B; IL6, interleukin 6; LIF, leukemia inhibitory factor; CNTF, ciliary neurotrophic factor; OsM, oncostatin M; CNV, choroidal neovascularization; NAC, N-acetyl cysteine; EGF, epidermal growth factor; GlcN, glucosamine

The retinal pigmented epithelium (RPE) is a monolayer of specialized epithelial cells located between the photoreceptors of the retina and the choroidal blood supply. The RPE is essential for maintaining retinal health and vision. Recent findings identified STAT3 as a newly recognized regulator of RPE survival, inflammatory response, visual cycle maintenance, and cytokine release. Additionally, STAT3 is implicated in retinal diseases that affect the RPE, including the common blinding disease age-related macular degeneration. Determining how STAT3 influences RPE functions ultimately may lead to novel therapeutics for retinal disease. In this review, we summarize the roles of JAK-STAT3 signaling in the RPE, and its potential contribution to retinal degenerations.

Introduction

The retina is a thin neural–epithelial tissue that lines the posterior region of the eye. The retina is primarily responsible for vision, and its cellular layers are specialized for converting photons of light to electrical signals that are perceived by the brain as color, contrast, depth and movement. Two major cell types in the retina contribute to vision: neurons detect and process light, and the adjacent RPE cells provide essential supportive functions. Dysfunction of either the neural layers or the RPE results in visual deficits of varying severity, and often leads to complete loss of vision. A major effort in the retina field is to characterize molecular and cellular mechanisms that regulate the function and survival of the RPE, and to understand processes that influence retina metabolism in its normal and pathological states. Recent evidence indicates that the JAK-STAT pathway plays important roles in the RPE during normal and diseased conditions. Accumulating data demonstrates that STAT3 integrates signals from the external environment, such as light, and the internal environment, such as inflammation, in order to regulate survival and biological activities of the RPE. Furthermore, several exciting studies demonstrate that STAT3 cross-talks with other signaling pathways in the RPE, such as Wnt signaling, toll-like receptor (TLR) signaling, and vascular endothelial growth factor (VEGF) signaling. Therefore, JAK-STAT signaling may be a central pathway in maintaining the health and function of the RPE, and consequently, of the retina, suggesting that STAT3 could be a potential therapeutic target for treating retinal degenerations.

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The Retinal Pigmented Epithelium (RPE) is Essential to the Function of the Retina

The RPE is a monolayer of tightly packed, interconnected epithelial cells that lies between the photoreceptor layer of the retina and the choroid blood supply. RPE cells are essential for vision by providing crucial support and maintenance functions for photoreceptors.[1] The RPE transports nutrients from the blood to the photoreceptors and the retina, including oxygen, fatty acids and retinol, and takes up metabolic end products from the retina and delivers them back into the circulation.[1,2] The RPE is also critical for maintaining the visual cycle by recycling components of phagocytosed photoreceptor outer segments.[3] Additional functions of the RPE include regulating pH balance, fluid uptake, growth factor secretion, and removing reactive oxygen species (ROS). As a result of the close interaction between RPE and photoreceptors, RPE dystrophy directly leads to photoreceptor death in humans and in animal models of retinal disease.[4] Indeed, RPE dysfunction is a primary cause of many retinal degenerative diseases, such as age-related macular degeneration (AMD).

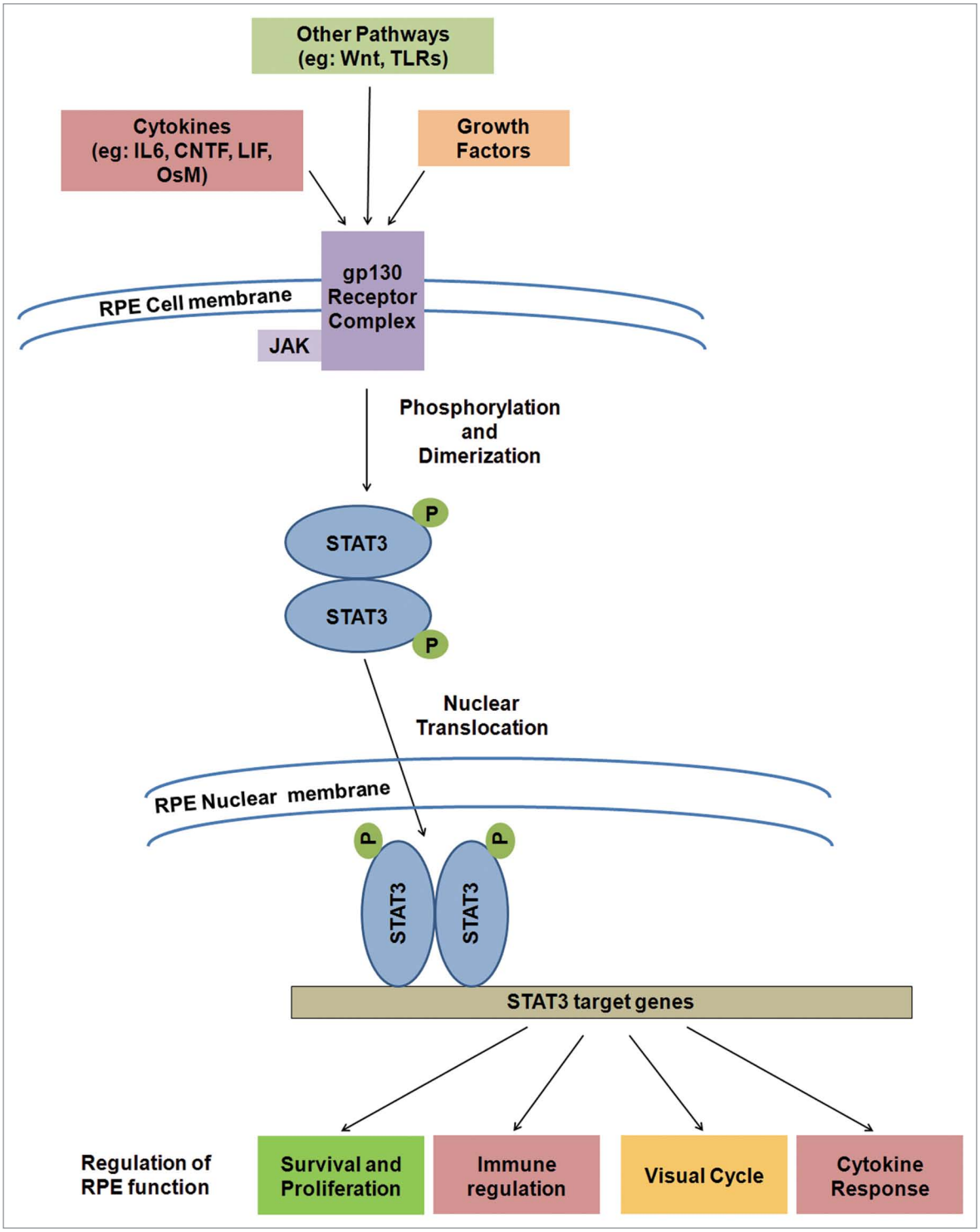

Figure 1. Functions of STAT3 in the RPE. Ligands bind to the gp130 receptor complex and activate JAK phosphorylation, leading to STAT3 phosphorylation and dimerization. The phosphorylated STAT3 dimer translocates to the nucleus and binds to the promoter of STAT3 target genes. In the RPE, STAT3 target genes can modulate RPE survival and proliferation, immune response, cytokine release, and visual cycle activity. Abnormal regulation of these pathways may be underlying causes of retinal diseases and degenerations.

Major Functions of STAT3

JAK-STAT3 signaling is activated by specific ligands, including growth factors and cytokines, which bind to JAK receptors (**Fig. 1**).[5,6] Upon initiation of STAT3 signaling, the STAT3 transcription factor is phosphorylated, leading to dimerization and translocation to the nucleus, where it binds to specific consensus sites within promoters of its target genes and activates

transcription. STAT3 activity is critical for a wide range of functions in numerous cell types, including cellular differentiation, cell-cycle progression, proliferation, and survival.[5-12] STAT3 also plays roles in regulating the immune response and inflammation.[13] Based on the various functions of STAT3 and its upstream ligands in other cell types, several candidate roles for STAT3 have been investigated in RPE to determine whether STAT3 activation regulates and integrates biological processes that are essential to the health of the retina. The roles of STAT3 in the RPE are described in detail below.

STAT3 Expression in the RPE

Within the eye, STAT3 plays an important role in the development of many ocular structures, including the lens and retina. Zhang et al. examined the expression of different STATs throughout the developing mouse eye.[14] Expression of STAT3 protein was noted first in the lens during early development, with onset beginning at embryonic day 11.5. STAT3 was observed in neurons in the differentiated inner retina starting at embryonic day 14.5, and then appeared in the outer retina (photoreceptors) and RPE beginning at postnatal day 1, and continuing to day 5, which corresponds to the phase of rapid differentiation of retinal progenitors. The expression of STAT3 in the outer retina is consistent with its critical role in regulating photoreceptor differentiation.[15] STAT3 acts as a negative regulator of rod photoreceptor differentiation and mediates the effects of ciliary neurotrophic factor (CNTF) on the retina. Inhibition of STAT3 was shown to dramatically alter the development of the outer retina.[15] STAT3 was detected in both the nucleus and cytoplasm of RPE cells during retinal development, unlike other STAT family members, which show only cytoplasmic expression.[14] In the adult retina, STAT3 is constitutively expressed in the RPE, as well as neurons in the ganglion and inner nuclear layers and Muller glia.[14,16] Phosphorylated STAT3 was also observed in the nucleus of the RPE cells, indicating that there is a basal level of STAT3 signaling in the adult retina. Interestingly, STAT3 is often upregulated and highly activated[16-18] during retinal disease, suggesting that STAT3 may play a role in disease progression or the intrinsic tissue survival response, as described in detail below.

Activities of STAT3 in the RPE

Survival. STAT3 is known to upregulate many pro-survival genes, such as survivin and Bcl-xl, in various cell types.[19,20] Consistent with a pro-survival activity of STAT3, upregulation of STAT3 was shown to protect RPE cells from injury.[6,12] We recently demonstrated that STAT3 mediated the Wnt-dependent protection of RPE cells during oxidative stress injury.[6] Furthermore, Wnt signaling increased total STAT3 and nuclear phosphorylated STAT3 levels. The importance of STAT3 to RPE survival was shown in experiments that used siRNA to silence STAT3, which eliminated the protective effect of Wnt signaling.[6] In another recent study, STAT3 was also shown to mediate the protective effect of innate immune signaling in the RPE.[12] Activation of the innate immunity receptor TLR3 led to time-dependent increases in total STAT3 and phosphorylated STAT3.[12] Furthermore, the protective effect of TLR3 activation against oxidative stress in RPE was also mediated though STAT3, suggesting that STAT3 serves to integrate immunity pathways with cell survival signaling. These results indicate that STAT3 is an important downstream mediator of RPE survival following injury, and can be activated through multiple pathways.

Immune regulatory role. An important function of the RPE is to secrete immunosuppressive factors and to absorb excess light and neutralize light-induced formation of free radicals.[1] Exposure of the retina to UV light is an established activator of various immune and inflammatory responses,[21-23] and recent findings implicate STAT3 in this process. Chou et al. showed that medial wave UV light (UVB) upregulated IL6 RNA and protein levels and STAT3 phosphorylation in a time-dependent manner in the RPE.[24] Furthermore, induction of STAT3 and IL6 by UVB led to an increase in complement factor B (CFB), which is a major component of the complement branch of the innate immune system. Inhibition of STAT3, using the JAK-STAT blocker AG490 or STAT3-specific shRNA, attenuated CFB elevation and RPE inflammatory signaling, indicating that STAT3 is a necessary component of the inflammatory response of the RPE. Therefore, these data are the first to link STAT3 with light-induced regulation of inflammation in the RPE. Although IL6 is an upstream activator of STAT3, it remains to be determined whether the regulation of STAT3 by UVB required IL6.

Regulation of the visual cycle. The RPE plays a critical role in the maintenance of vision by recycling retinal chromophores.[1,25] The rate of chromophore production is important for retinal function because too little or too much chromophore leads to retinal degeneration.[26-28] A key enzyme in the reconversion of all-*trans* retinal back to its *x*-retinal form is RPE65.[29,30] Interestingly, STAT3 activation was recently associated with RPE65 levels, suggesting a role for STAT3 in regulating the visual cycle.[28] Chuchair-Elliot et al. showed that intravitreally injected leukemia inhibitory factor (LIF) activated STAT3 in the mouse RPE, which led to significantly reduced RPE65 expression. The regulation of RPE65 was shown to be STAT3 dependent through the use of conditional knockout mice that lack STAT3 specifically in the RPE.[28] Because the maintenance of the visual cycle and proper RPE function are essential for vision, these findings indicate an important activity for STAT3 in vision.

Cytokine response. The RPE is responsive to multiple cytokines and growth factors, and many of these signal through STAT3.[5,13,31] Activation of STAT3 by cytokines leads to various effects on the RPE, including proliferation, fluid transport, cytokine and growth factor secretion, and visual cycle maintenance. CNTF, LIF, and oncostatin M (OsM) are all members of the IL6 family and bind to several types of receptors that initiate JAK-STAT3 signaling in RPE.[32] Interestingly, the activation of STAT3 by these cytokines shows specific cellular polarization properties. For example, OsM increased STAT3 activation differentially on the apical (photoreceptor) side of the RPE, in contrast to CNTF, which increased STAT3 phosphorylation in both the apical and basal (blood) sides.[33] Although it is not yet understood why these cytokines cause directional activation of STAT3,

we speculate that one possible reason is that differential localization of STAT3 phosphorylation may contribute to activating or altering RPE functions that are polarized, such as ion and fluid transport and visual molecule recycling. An additional point of interest is that the downstream activities of these cytokines differ, despite their common activation of STAT3. While CNTF increases RPE cell survival, it had no effect on cellular proliferation, while OsM decreased both cell survival and proliferation.[33] CNTF also increased transepithelial fluid transport across the RPE, which was shown to be mediated by the JAK-STAT3 pathway through the use of specific inhibitors.[33]

Potential Roles of STAT3 in RPE Pathology during Retinal Disease

Age-related macular degeneration (AMD) is a progressive, irreversible degenerative disease of the macula that causes severe central visual loss. It occurs frequently in adults over the age of 60 and is the most common cause of blindness in developed countries.[34,35] Early stage AMD is characterized by RPE abnormalities leading to photoreceptor dysfunction. Although the exact pathogenesis of AMD is unknown, molecular and cellular damage in RPE cells that is caused by oxidative stress is believed to be a major contributor to pathology.[36] In neovascular AMD, new blood vessel formation within the choroid occurs. These new vessels are leaky, which causes subretinal hemorrhage and subsequent fibrovascular membrane formation, resulting in progressive and irreversible visual loss.[37] Investigating the mechanism of choroidal neovascular (CNV) membrane formation and RPE abnormalities will enable understanding of the molecular pathogenesis involved in AMD.

Several lines of evidence have associated STAT3 with CNV in AMD. STAT3 is a critical transcriptional mediator of the angiogenic factor VEGF.[38] VEGF is an inducer of CNV in AMD eyes, and blocking VEGF activity is the primary therapeutic strategy for treating neovascular AMD. Additionally, activated STAT3 was localized to RPE cells overlying areas of CNV in eyes of patients with AMD.[17] STAT3 was mainly identified in areas of developing scar tissue that were rich in RPE cells, fibroblasts, macrophages, and lymphocytes, and was absent from avascular scar tissue and control eyes without AMD.[17] Therefore, the activation of STAT3 in RPE cells adjacent to developing CNV scar tissue is compelling associative evidence for a role of STAT3 in the formation of CNV membrane and/or the subsequent reactive tissue response. Although it is unclear whether irregular STAT3 activation induces CNV or if CNV induces increased STAT3 signaling, the following studies suggest the former, rather than latter, possibility.

The presence of macrophages and lymphocytes indicates a role of inflammation in the formation of CNV, and STAT3 has been implicated as a regulator of the inflammatory response in the RPE.[24] Indeed, the pro-inflammatory cytokine IL6, a ligand activator of STAT3, was elevated in serum of AMD patients.[39] Also, using a murine laser-induced CNV model, Izumi-Nagai et al. demonstrated that CNV induction stimulated IL6 expression and activation of STAT3 in the RPE-choroid complex, as measured by increased phosphorylated STAT3 protein.[40] Furthermore, inhibiting IL6 receptor signaling using the IL6 receptor monoclonal antibody MR16-1 significantly suppressed STAT3 phosphorylation and was associated with suppression of CNV formation. Pharmacological blockage of STAT3 via the JAK-STAT pathway using the JAK inhibitor AG490 also significantly and consistently suppressed CNV. In summary, this important study confirmed that IL6 receptor mediated activation of STAT3 plays a significant role in the formation of CNV in the mouse.

Another line of evidence for the involvement of STAT3 in CNV is the association between STAT3, VEGF, and hyperglycemia. Li et al. demonstrated that induction of VEGF in a cellular model of hyperglycemia was correlated with STAT3 activation in cultured RPE cells.[41] Phosphorylated STAT3 protein significantly increased in a time-dependent manner, reaching maximum levels after 3 h of exposure to high-glucose medium. VEGF mRNA was also upregulated during high-glucose exposure and the time-course of this upregulation was similar to that of STAT3. The increase in STAT3 in RPE by hyperglycemia may potentially be a cellular protective response, which would be consistent with findings by our group and others that demonstrated that STAT3 protects cells from injury.[6,8,12]

The Li et al. study also investigated the relationship between oxidative stress and STAT3 activation. Oxidative stress has been implicated as a contributor of CNV in AMD.[42] It has also been previously demonstrated that an increase in superoxide production in the retina caused by hyperglycemia contributes to the pathogenesis of diabetic retinopathy.[43] N-acetyl cysteine (NAC) is a thiol-containing compound that has been used as an anti-oxidant to counteract oxidative stress in several diseases. Li et al. demonstrated that treating an RPE cell line with NAC while in a high-glucose medium reduced phosphorylated STAT3 protein levels and VEGF expression. Moreover, treatment with the JAK-STAT3 pathway inhibitor AG490 also reduced VEGF levels. Therefore, anti-oxidant therapy reduced VEGF/STAT3 signaling, which suggests an upstream role of oxidative stress in the STAT3 pathway. Because STAT3 protects RPE from oxidative stress,[6,12] the Li study suggests a complex signaling pathway by which oxidative stress and STAT3 are co-regulated.

Another retinal disease that involves the RPE is proliferative vitreoretinopathy, which occurs when the RPE has accelerated proliferation and migration, and which leads to retinal detachments and blindness.[44] RPE proliferation is related to epidermal growth factor (EGF) signaling, which has been linked to STAT3 activation.[45] EGF signaling increased STAT3, ERK1/2, and AKT phosphorylation in a dose-dependent manner in RPE cells, leading to increased proliferation in vitro. Furthermore, the carbohydrate glucosamine (GlcN) inhibited STAT3 phosphorylation and reduced RPE proliferation.[46]

Future Directions

Although analysis of the functional role of STAT3 in RPE biology is a relatively new field, there are already several major findings, including the regulation of RPE survival, proliferation,

inflammation, and visual cycle function by STAT3. These functions of STAT3 may have important clinical implications in various retinal degenerations, such as AMD, diabetic retinopathy, and proliferative vitreoretinopathy. However, despite recent progress, there are several notable challenges that still need to be solved. Identifying target genes of STAT3 that mediate its effects will be essential for properly understanding the mechanism of action of STAT3 in the RPE and retina. Also, the activators of STAT3 in the RPE are mostly unknown, with the notable exceptions of IL6, Wnt, and VEGF. Finally, STAT3 cross-talk with other major signaling pathways in RPE is only just beginning to be recognized (for example, its interactions with Wnt and TLR3), and further examination of STAT3 interactions with other pathways will reveal a great deal about its regulation. Because STAT3 regulates the survival of other cell types, particularly cancer cells, there are already major efforts focused on finding specific targets to interfere with STAT3 signaling. Therefore, potential future therapeutic strategies may involve delivering highly specific STAT3 regulators to diseased RPE cells, in order to delay or halt the progression of retinal degenerations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Strauss O. The retinal pigment epithelium in visual function. Physiol Rev 2005; 85:845-81; PMID:15987797; http://dx.doi.org/10.1152/physrev.00021.2004
2. Strauss O. The Retinal Pigment Epithelium. 1995.
3. Baehr W, Wu SM, Bird AC, Palczewski K. The retinoid cycle and retina disease. Vision Res 2003; 43:2957-8; PMID:14611932; http://dx.doi.org/10.1016/j.visres.2003.10.001
4. Marmorstein AD, Finnemann SC, Bonilha VL, Rodriguez-Boulan E. Morphogenesis of the retinal pigment epithelium: toward understanding retinal degenerative diseases. Ann N Y Acad Sci 1998; 857:1-12; PMID:9917828; http://dx.doi.org/10.1111/j.1749-6632.1998.tb10102.x
5. Aaronson DS, Horvath CM. A road map for those who don't know JAK-STAT. Science 2002; 296:1653-5; PMID:12040185; http://dx.doi.org/10.1126/science.1071545
6. Fragoso MA, Patel AK, Nakamura RE, Yi H, Surapaneni K, Hackam AS. The Wnt/β-catenin pathway cross-talks with STAT3 signaling to regulate survival of retinal pigment epithelium cells. PLoS One 2012; 7:e46892; PMID:23056515; http://dx.doi.org/10.1371/journal.pone.0046892
7. Akira S. Roles of STAT3 defined by tissue-specific gene targeting. Oncogene 2000; 19:2607-11; PMID:10851059; http://dx.doi.org/10.1038/sj.onc.1203478
8. Barry SP, Townsend PA, McCormick J, Knight RA, Scarabelli TM, Latchman DS, et al. STAT3 deletion sensitizes cells to oxidative stress. Biochem Biophys Res Commun 2009; 385:324-9; PMID:19450559; http://dx.doi.org/10.1016/j.bbrc.2009.05.051
9. Haricharan S, Li Y. STAT signaling in mammary gland differentiation, cell survival and tumorigenesis. Mol Cell Endocrinol 2013; In press; PMID:23541951; http://dx.doi.org/10.1016/j.mce.2013.03.014
10. Xiong H, Zhang ZG, Tian XQ, Sun DF, Liang QC, Zhang YJ, et al. Inhibition of JAK1, 2/STAT3 signaling induces apoptosis, cell cycle arrest, and reduces tumor cell invasion in colorectal cancer cells. Neoplasia 2008; 10:287-97; PMID:18320073
11. Nichane M, Ren X, Bellefroid EJ. Self-regulation of Stat3 activity coordinates cell-cycle progression and neural crest specification. EMBO J 2010; 29:55-67; PMID:19851287; http://dx.doi.org/10.1038/emboj.2009.313
12. Patel AK, Hackam AS. Toll-like receptor 3 (TLR3) protects retinal pigmented epithelium (RPE) cells from oxidative stress through a STAT3-dependent mechanism. Mol Immunol 2013; 54:122-31; PMID:23267850; http://dx.doi.org/10.1016/j.molimm.2012.11.005
13. Aggarwal BB, Kunnumakkara AB, Harikumar KB, Gupta SR, Tharakan ST, Koca C, et al. Signal transducer and activator of transcription-3, inflammation, and cancer: how intimate is the relationship? Ann N Y Acad Sci 2009; 1171:59-76; PMID:19723038; http://dx.doi.org/10.1111/j.1749-6632.2009.04911.x
14. Zhang SS, Wei JY, Li C, Barnstable CJ, Fu XY. Expression and activation of STAT proteins during mouse retina development. Exp Eye Res 2003; 76:421-31; PMID:12634107; http://dx.doi.org/10.1016/S0014-4835(03)00002-2
15. Zhang SS, Wei J, Qin H, Zhang L, Xie B, Hui P, et al. STAT3-mediated signaling in the determination of rod photoreceptor cell fate in mouse retina. Invest Ophthalmol Vis Sci 2004; 45:2407-12; PMID:15223824; http://dx.doi.org/10.1167/iovs.04-0003
16. Peterson WM, Wang Q, Tzekova R, Wiegand SJ. Ciliary neurotrophic factor and stress stimuli activate the Jak-STAT pathway in retinal neurons and glia. J Neurosci 2000; 20:4081-90; PMID:10818143
17. Fasler-Kan E, Wunderlich K, Hildebrand P, Flammer J, Meyer P. Activated STAT 3 in choroidal neovascular membranes of patients with age-related macular degeneration. Ophthalmologica 2005; 219:214-21; PMID:16088240; http://dx.doi.org/10.1159/000085730
18. Zhang C, Li H, Liu MG, Kawasaki A, Fu XY, Barnstable CJ, et al. STAT3 activation protects retinal ganglion cell layer neurons in response to stress. Exp Eye Res 2008; 86:991-7; PMID:18471811; http://dx.doi.org/10.1016/j.exer.2008.03.020
19. Gritsko T, Williams A, Turkson J, Kaneko S, Bowman T, Huang M, et al. Persistent activation of stat3 signaling induces survivin gene expression and confers resistance to apoptosis in human breast cancer cells. Clin Cancer Res 2006; 12:11-9; PMID:16397018; http://dx.doi.org/10.1158/1078-0432.CCR-04-1752
20. Battle TE, Frank DA. The role of STATs in apoptosis. Curr Mol Med 2002; 2:381-92; PMID:12108949; http://dx.doi.org/10.2174/1566524023362456
21. Higgins GT, Wang JH, Dockery P, Cleary PE, Redmond HP. Induction of angiogenic cytokine expression in cultured RPE by ingestion of oxidized photoreceptor outer segments. Invest Ophthalmol Vis Sci 2003; 44:1775-82; PMID:12657621; http://dx.doi.org/10.1167/iovs.02-0742
22. Lu H, Hunt DM, Ganti R, Davis A, Dutt K, Alam J, et al. Metallothionein protects retinal pigment epithelial cells against apoptosis and oxidative stress. Exp Eye Res 2002; 74:83-92; PMID:11878821; http://dx.doi.org/10.1006/exer.2001.1101
23. Roduit R, Schorderet DF. MAP kinase pathways in UV-induced apoptosis of retinal pigment epithelium ARPE19 cells. Apoptosis 2008; 13:343-53; PMID:18253836; http://dx.doi.org/10.1007/s10495-008-0179-8
24. Chou WW, Wang YS, Chen KC, Wu JM, Liang CL, Juo SH. Tannic acid suppresses ultraviolet B-induced inflammatory signaling and complement factor B on human retinal pigment epithelial cells. Cell Immunol 2012; 273:79-84; PMID:22169226; http://dx.doi.org/10.1016/j.cellimm.2011.11.003
25. Sparrow JR, Hicks D, Hamel CP. The retinal pigment epithelium in health and disease. Curr Mol Med 2010; 10:802-23; PMID:21091424; http://dx.doi.org/10.2174/156652410793937813
26. Maeda A, Maeda T, Golczak M, Chou S, Desai A, Hoppel CL, et al. Involvement of all-trans-retinal in acute light-induced retinopathy of mice. J Biol Chem 2009; 284:15173-83; PMID:19304658; http://dx.doi.org/10.1074/jbc.M900322200
27. Shiose S, Chen Y, Okano K, Roy S, Kohno H, Tang J, et al. Toll-like receptor 3 is required for development of retinopathy caused by impaired all-trans-retinal clearance in mice. J Biol Chem 2011; 286:15543-55; PMID:21383019; http://dx.doi.org/10.1074/jbc.M111.228551
28. Chucair-Elliott AJ, Elliott MH, Wang J, Moiseyev GP, Ma JX, Politi LE, et al. Leukemia inhibitory factor coordinates the down-regulation of the visual cycle in the retina and retinal-pigmented epithelium. J Biol Chem 2012; 287:24092-102; PMID:22645143; http://dx.doi.org/10.1074/jbc.M112.378240
29. Morimura H, Fishman GA, Grover SA, Fulton AB, Berson EL, Dryja TP. Mutations in the RPE65 gene in patients with autosomal recessive retinitis pigmentosa or leber congenital amaurosis. Proc Natl Acad Sci U S A 1998; 95:3088-93; PMID:9501220; http://dx.doi.org/10.1073/pnas.95.6.3088
30. Redmond TM, Yu S, Lee E, Bok D, Hamasaki D, Chen N, et al. Rpe65 is necessary for production of 11-cis-vitamin A in the retinal visual cycle. Nat Genet 1998; 20:344-51; PMID:9843205; http://dx.doi.org/10.1038/3813
31. Akira S. Functional roles of STAT family proteins: lessons from knockout mice. Stem Cells 1999; 17:138-46; PMID:10342556; http://dx.doi.org/10.1002/stem.170138
32. Taga T, Kishimoto T. Gp130 and the interleukin-6 family of cytokines. Annu Rev Immunol 1997; 15:797-819; PMID:9143707; http://dx.doi.org/10.1146/annurev.immunol.15.1.797
33. Li R, Wen R, Banzon T, Maminishkis A, Miller SS. CNTF mediates neurotrophic factor secretion and fluid absorption in human retinal pigment epithelium. PLoS One 2011; 6:e23148; PMID:21912637; http://dx.doi.org/10.1371/journal.pone.0023148
34. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 1992; 99:933-43; PMID:1630784

35. Klein R, Wang Q, Klein BE, Moss SE, Meuer SM. The relationship of age-related maculopathy, cataract, and glaucoma to visual acuity. Invest Ophthalmol Vis Sci 1995; 36:182-91; PMID:7822146
36. Liang FQ, Godley BF. Oxidative stress-induced mitochondrial DNA damage in human retinal pigment epithelial cells: a possible mechanism for RPE aging and age-related macular degeneration. Exp Eye Res 2003; 76:397-403; PMID:12634104; http://dx.doi.org/10.1016/S0014-4835(03)00023-X
37. Ng EW, Adamis AP. Targeting angiogenesis, the underlying disorder in neovascular age-related macular degeneration. Can J Ophthalmol 2005; 40:352-68; PMID:15947805
38. Xu Q, Briggs J, Park S, Niu G, Kortylewski M, Zhang S, et al. Targeting Stat3 blocks both HIF-1 and VEGF expression induced by multiple oncogenic growth signaling pathways. Oncogene 2005; 24:5552-60; PMID:16007214; http://dx.doi.org/10.1038/sj.onc.1208719
39. Seddon JM, George S, Rosner B, Rifai N. Progression of age-related macular degeneration: prospective assessment of C-reactive protein, interleukin 6, and other cardiovascular biomarkers. Arch Ophthalmol 2005; 123:774-82; PMID:15955978; http://dx.doi.org/10.1001/archopht.123.6.774
40. Izumi-Nagai K, Nagai N, Ozawa Y, Mihara M, Ohsugi Y, Kurihara T, et al. Interleukin-6 receptor-mediated activation of signal transducer and activator of transcription-3 (STAT3) promotes choroidal neovascularization. Am J Pathol 2007; 170:2149-58; PMID:17525280; http://dx.doi.org/10.2353/ajpath.2007.061018
41. Li X, Cai Y, Wang YS, Shi YY, Hou W, Xu CS, et al. Hyperglycaemia exacerbates choroidal neovascularisation in mice via the oxidative stress-induced activation of STAT3 signalling in RPE cells. PLoS One 2012; 7:e47600; PMID:23094067; http://dx.doi.org/10.1371/journal.pone.0047600
42. Dong A, Xie B, Shen J, Yoshida T, Yokoi K, Hackett SF, et al. Oxidative stress promotes ocular neovascularization. J Cell Physiol 2009; 219:544-52; PMID:19142872; http://dx.doi.org/10.1002/jcp.21698
43. Du Y, Miller CM, Kern TS. Hyperglycemia increases mitochondrial superoxide in retina and retinal cells. Free Radic Biol Med 2003; 35:1491-9; PMID:14642397; http://dx.doi.org/10.1016/j.freeradbiomed.2003.08.018
44. Pastor JC. Proliferative vitreoretinopathy: an overview. Surv Ophthalmol 1998; 43:3-18; PMID:9716190; http://dx.doi.org/10.1016/S0039-6257(98)00023-X
45. Chen Z, Chen CZ, Gong WR, Li JP, Xing YQ. Integrin-alpha5 mediates epidermal growth factor-induced retinal pigment epithelial cell proliferation and migration. Pathobiology 2010; 77:88-95; PMID:20332668; http://dx.doi.org/10.1159/000278290
46. Liang CM, Tai MC, Chang YH, Chen YH, Chen CL, Chien MW, et al. Glucosamine inhibits epidermal growth factor-induced proliferation and cell-cycle progression in retinal pigment epithelial cells. Mol Vis 2010; 16:2559-71; PMID:21151603