Potential drug interventions for diabetic retinopathy

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Diabetic retinopathy (DR) is of great interest to the drug discovery community owing to the rising worldwide prevalence of diabetes and its associated complications. The complex molecular mechanism associated with DR development and the poor translatability of available animal models to late-stage DR are considered to be major hurdles for drug discovery. Here we will provide an overview of the mechanistic rationale as well as clinical efficacy of drug candidates, and highlight emerging and potential targets for therapeutic intervention at different stages of DR.

Diabetic retinopathy (DR) is a diabetic complication resulting from microvascular retinal changes and is a leading cause of blindness in Europeans and Americans. DR takes many years to develop, and is separated into nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) stages. NPDR is mainly characterized by vascular damage, such as capillary apoptosis and degeneration, and increased vascular permeability. By contrast, PDR is characterized by abnormal growth of fragile blood vessels on the retina and posterior surface of the vitreous [1]. All stages of retinopathy can be associated with diabetic macular edema (DME). Most DR drug discovery efforts have focused on addressing the pathological angiogenesis and macular edema that ultimately lead to blindness [2].

The likelihood of developing DR is positively correlated with how long the patient in question has had either type I or type II diabetes. Recently, a pooled analysis, including 35 studies worldwide with 22,896 diabetic subjects showed that the prevalence in diabetic patients was 35.4% for any stage of DR, 7.24% for PDR and 7.48% for DME [3]. Extrapolating these prevalence rates to the world diabetes population, it is estimated that in 2010 92.6 million adults had a stage of DR, 17.2 million had PDR and 20.6 million had DME. The DR population is expected to increase in parallel with the rising incidence of diabetes mellitus. Globally, as of 2010, an estimated 285 million people had diabetes. Its incidence is increasing rapidly and by 2030 this number is estimated to almost double [4].

So far, the treatments for DR have relied almost exclusively on metabolic control, especially intensive control of hyperglycemia, until the severity of vascular lesions warrant laser surgery or, more recently, intravitreous injection of anti-vascular endothelial growth factors (VEGFs) [5]. With the purpose of identifying potential targets for DR treatments, preclinical studies are actively underway in animal models of diabetes and oxygen-induced retinopathy. Within the context of the molecular pathogenesis of DR, many pharmacologic agents are under active development preclinically or clinically for the treatment of DR. This review will provide an overview of the drug candidates and targets that are currently being, or recently have been (Table 1), pursued for DR treatment; and their associated mechanistic rationale and efficacy evaluations based on existing clinical results.

Pathology

DR initially develops as a result of hyperglycemia-induced microvascular and neural damage, via a complex interaction of glucose-associated pathway fluxes [e.g. polyol, hexosamine, protein kinase C (PKC), poly(ADPribose) polymerase (PARP) and advanced glycation endproducts/receptor for advanced glycation endproducts (AGE/RAGE) pathways], reactive oxygen species (ROS), activated signaling pathways (e.g. RAS/RAF/MAPK, PI3K/AKT/mTOR and JNK/STAT), and concomitant transcription of growth factors and cytokines (Fig. 1) [6–9]. Ultimately, as DR progresses, ischemia occurs and leads to the retinal neovascularization and vision

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TABLE 1

Targets and/or agents for diabetic retinopathy treatment

Intervention type	Target/drug candidate	Generic name of agents (PubChem CID is provided for small molecules)	Agent type	Highest status/clinical trial
Glucotoxic pathway fluxes inhibitor	Advanced glycation endproduct (AGE) inhibitors; nitric oxide synthase (NOS) inhibitors	Pimagedine (CID 2146)	Small molecule (SM)	Phase III for diabetic retinopathy (DR) treatment
	Receptor for advanced glycation endproduct (RAGE) antagonists	TTP488[a]	SM	Phase II for diabetic nephropathy treatment
	Aldose reductase	Sorbinil (CID 337359)	SM	Phase III for DR treatment, discontinued
	Protein kinase C β(PKC β) inhibitors	Ruboxistaurin (CID 153999)	SM	Phase III for DR treatment
Antioxidation	Reactive oxygen species (ROS) inhibitors	Calcium dobesilate (CID 29963)	SM	Phase IV for DR treatment
	Lipid peroxidation inhibitors	Anisodamine (CID 64704)	SM	Preclinical
Inhibitors of signal transduction pathways	Mammalian target of rapamycin (mTOR) inhibitors; immunosuppressive agents	Sirolimus (CID 5284616)	SM	Phase II for diabetic macular edema (DME) and DR treatment
	mTOR inhibitors	SG00529 (CID 11998575)	SM	Preclinical
	Raf kinase inhibitors	ISIS13650	DNA	Phase II for DME treatment
Adhesion inhibition	Integrin αLβ2 inhibitors	Lifitegrast (CID 11965427)	SM	Preclinical
	Integrin αVβ3, integrin αVβ5 inhibitors	JNJ26076713 (CID 24752877); PS680648 (CID 25211781); CID 59702242; CID 59702263	SM	Preclinical
	Integrin αVβ3, integrin αIIbβ3 inhibitors	Saxatilin	Polypeptides	Preclinical
Anti-inflammation	Interleukin-1 beta (IL-1β) inhibitors	Canakinumab	Monoclonal antibodies (mAbs)	Phase I for angiogenesis treatment in proliferative diabetic retinopathy (PDR)
	Anti-tumor necrosis factor alpha (TNFα) antibodies	Infliximab	mAbs	Phase III for refractory DME treatment, terminated
	TNFα, IL-1β inhibitors	FID201273 (CID 9822803)	SM	Preclinical
Cytokines/growth factor modulators	Pigment epithelium-derived factor (PEDF) vector	AdPEDF	Vector	Phase I for neovascular age-related macular degeneration (NAMD) treatment
	PEDF polypeptides	PEDF	Polypeptides	Preclinical
	Tie2 agonist	AKB9778[a]	SM	Phase I/II for DME treatment
	Tie2 agonist	PubChem CID 71433909	SM	Preclinical for DR treatment
	Anti-vascular endothelial growth factor (VEGF) antibodies	Bevacizumab (BEV)	mAbs	Phase II/III for DME and PDR treatment
	Anti-VEGFa antibodies	Ranibizumab (RAB)	mAbs	Launched for DME treatment, Phase III for DR treatment
	Anti-VEGF peptides	Aflibercept	Polypeptides	Phase III for DME treatment
	VEGF interfering RNA	Bevasiranib	RNA	Phase II for DME treatment
	VEGF interfering RNA	Pegaptanib	Pegylated RNA	Phase III for DME treatment
	VEGFA expression inhibitors	MP0112	Polypeptides	Phase I/II for DME treatment, terminated
	Hypoxia-inducible gene RTP-801 expression inhibitors	PF655	Small interfering RNA (SiRNAs)	Phase II for DME treatment
Hormone modulators	Glucocorticoid steroid analogs	Triamcinolone acetonide; triamcinolone	Glucocorticoid steroid	Launched for DME treatment
		Fluocinolone acetonide	Glucocorticoid steroid	Launched for DME treatment
		Nova63035	Corticosteroid prodrug	Phase I for DME treatment
	Tetrapeptide based on epithalamin	Epithalon	Oligopeptides	Phase I/II for DME treatment
	TNFα modulators	Danazol	Androgens	Phase II for DME treatment
	Somatostatin SRIF1A (sst2) analogs	Octreotide acetate	Oligopeptides	Phase III for PDR treatment
		CID 52936725; CID 52936721	SM	Preclinical

[a] Structures not released.