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Pathophysiology of diabetic retinopathy: Contribution and limitations of laboratory research

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Abstract

Preclinical models of diabetic retinopathy are indispensable in the drug discovery and development of new therapies. They are, however, imperfect facsimiles of diabetic retinopathy in humans. This chapter discusses the advantages, limitations, physiological and pathological relevance pre-clinical models of diabetic retinopathy. The judicious interpretation and extrapolation of data derived from these models to humans, and a correspondingly greater emphasis placed on translational medical research in early stage clinical trials, are essential to more successfully inhibit the development and progression of diabetic retinopathy in the future.

It is generally accepted that animal models do not perfectly represent human conditions, and this is true also for diabetic retinopathy. Thus, a reasonable question is how closely the laboratory models of diabetic retinopathy mimic the human disease, and how that influences our willingness to use and believe data from such animal models. Animal models do have important advantages in providing mechanistic insight and when assessing potential new treatments with unknown long-term adverse effects. However when a proposed treatment is known to be essentially free of safety concerns or adverse effects (such as an off-label use of an FDA approved drug), it can be validly questioned as to why laboratory animal models should be used.

Specifically with respect to diabetic retinopathy, the deficiencies of most species of small animals used for laboratory research include the apparent failure to develop diabetes-induced pre-retinal neovascularization and clinically meaningful stages of the retinopathy, the lack of a macula, and the apparent failure of most models to develop diabetes-induced retinal/macular thickening and edema. Other potential weaknesses compared to humans include the fundamental difference that most rodents are nocturnal, have a short lifespan (which affects

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the development of disease severity), have a very small retina, lack many of the lifestyle factors that can adversely affect human disease, and are unable to communicate about what they are or are not seeing (visual function).

Animal models do have important advantages, however. They require much less time and effort to obtain results than human clinical trials, and are considerably less expensive to conduct. Those potential advantages are not meaningful, however, unless the disease processes leading to retinopathy in animals are generally similar to those in diabetic patients

The available evidence suggests that the steps along the progression of diabetic retinopathy in the animal species tested are similar to humans, except that the animals do not progress as far along those steps as the longer-lived humans (Fig 1). Capillary degeneration, loss of pericytes, thickening of vascular basement membranes, as well as functional changes including changes in blood flow, visual function and vascular permeability develop in diabetic rodents, just as they do in longer-lived diabetic dogs, and even longer-lived diabetic primates and patients. Larger and longer-lived species (dogs [1–3], cats [4], primates [5,6] and humans) progress beyond those early lesions, and also develop microaneurysms, cotton-wool spots, IRMA, and at least in diabetic dogs [7] and primates [8,9], also retinal edema and/or intra-retinal neovascularization. To date, only humans have been found to develop pre-retinal neovascularization due to diabetes, typically after durations of diabetes that are considerably longer than can be studied in any animal species.

Have animal studies of diabetic retinopathy been reliable at predicting the response of diabetic patients to disease or therapy? Animal models have been studied using similar therapies as diabetic patients in only a limited number of cases (in large part due to the extraordinary cost of clinical trials related to diabetic retinopathy), but some comparisons can be made. A good example of animal studies predicting the response of diabetic patients to therapy is the demonstration of the beneficial effect of glycemic control on diabetic retinopathy in 5 year studies of diabetic dogs, which pre-dated the later demonstration of a similar benefit of glycemic control in diabetic patients by more than a decade [10]. Studies in dogs [11,12] and then also rats [13,14] demonstrated a resistance of the retinopathy to arrest with treatment once the retinopathy had been initiated (later known as metabolic memory) that was found also in humans [15]. Studies in diabetic dogs [16] as well as diabetic patients [17] also showed no beneficial effect of an aldose reductase inhibitor to inhibit initiation or progression of the microaneurysms and capillary degeneration that characterize diabetic retinopathy. However, results related to aldose reductase and retinopathy differed from human findings in diabetic mice [18,19] or some [20–22] (but not all [16,23]) galactose-feeding studies. Administration of aspirin was reported to inhibit the development or progression of diabetic retinopathy in dogs and rats [24,25] and in one study of diabetic patients [26], but not in another 2 year clinical study (Early Treatment of Diabetic Retinopathy; ETDRS) [27]. This difference might have been due to experimental design, because the animal studies showing a beneficial effect of the aspirin used higher (potentially anti-inflammatory) doses of the drug than the ETDRS study, which used only a lower (anti-platelet) dose.

All-in-all, the evidence suggests that at least dogs and perhaps other long-lived mammals have shown value in terms of predicting the outcome of similar studies in diabetic patients, suggesting that the pathogenesis of the retinopathy in those species is similar to that in human patients.

The evidence that rodents show the same predictive ability with respect to the effect of a therapy on the development of retinal histopathology is less compelling, but there is evidence that diabetes induces abnormalities in retinal vascular permeability and visual function like those seen in diabetic patients. Also, molecular abnormalities in the retina are shared in common between diabetic patients and diabetic rodents. Moreover, diabetes-induced alterations in visual function (which has not been measured to date in large animals) becomes impaired in diabetic rodents [28,29], as it does in diabetic patients, providing some evidence that the rodent animal models also offer a meaningful opportunity to investigate the pathogenesis and treatment of the retinopathy that develops in diabetic patients.

A significant value of animal models is their use to clarify molecular mechanisms by which diseases progress and to provide insight into molecular mechanisms underlying effects of a therapy. Accordingly, what have animal studies revealed about the pathogenesis and pathophysiology of diabetic retinopathy? Initial studies using experimental hyperglycemia (such as with fructose [30,31] or galactose feeding [16,32–36]) clearly showed that hyperglycemia (as opposed to the insulin resistance or deficiency) plays a major role in the pathogenesis of the retinopathy in a way that could not be demonstrated in diabetic patients. Beyond that, many biochemical abnormalities have been detected in retinas of diabetic animals, presumably developing as a result of abnormalities in substrate availability (glucose and lipids) and hormonal abnormalities (insulin, growth hormone) acting systemically as well as on the retina [37–42], and the animal models clearly are central in elucidating the potential importance of these abnormalities in the development of the retinopathy. In addition, the development of the retinal vasculature after birth in the mouse combined with the development of endothelial specific Cre recombinases has provided an unprecedented opportunity to explore retinal vascular development and differentiation, thus providing the mechanistic framework from which therapies targeting vessel growth and remodeling have been made. Additional studies into the mechanisms of retinal function, signal transduction and differentiation continue to provide novel insight.

Probably the most impressive success story in the past decades with regard to diabetic retinopathy has been the remarkable effects of anti-VEGF (vascular endothelial growth factor) therapies to inhibit retinal neovascularization and reverse macular edema in diabetes and other diseases. These therapies currently are the only approved intervention for existing advanced diabetic retinopathy. Clinical research played a large role in identifying how best to use this therapeutic approach, but animal research played a huge role in identifying and characterizing VEGF, and demonstrating the relationship between VEGF and ischemia [43–48]. These therapies were developed largely as anti-cancer drugs, but were found to be effective in models of neovascularization in mice, and were supported by years of angiogenesis research including gene deletion studies and the use of VEGF-binding antibodies and soluble receptors [49].

A previously mentioned proof-of principal study was the demonstration of the beneficial effect of good glycemic control on the development of diabetic retinopathy prior to comparable convincing data in humans. A good example of animal studies demonstrating the molecular mechanisms underlying a therapy is the work that was done to understand the unexpected finding that diabetic retinopathy was significantly inhibited in patients treated with fibrates [50,51]. The mechanism of effect was judged not to be via lowering of lipids (as originally assumed), and subsequent animal studies demonstrated a variety actions of the fibrates on metabolism and transcription factors, as well as anti-oxidant and anti-inflammatory actions [52–56]. Animal models are providing insight also into the role of photoreceptors in the pathogenesis of both to the early and late stages of diabetic retinopathy (in part via release of soluble factors [57–61]), which follows from the clinical recognition that diabetic patients with retinitis pigmentosa seemed protected from the development of diabetic retinopathy [62].

For many years, many therapeutic studies were conducted in animal models with the assumption that a single (unidentified) molecular defect or pathway occurring in the retina in diabetes was a major cause of the retinopathy, and that inhibition of that abnormality or pathway would lead to inhibition of the retinopathy [16,24,25,63–77]. Indeed, a large number of animal studies using systemic pharmacologic therapies or genetically modified animals have demonstrated impressive inhibition of diabetes-induced abnormalities in retinal function or capillary permeability or degeneration at a particular duration of diabetes.

Should confidence in the animal models be reduced by the fact that many experimental therapies administered to animal models reportedly show a beneficial effect on lesions of the retinopathy, compared to the paucity of beneficial therapies clinically to inhibit early stages of the retinopathy? Caution is obviously warranted, since most studies neither tested the longevity of the beneficial effect, nor the effect of the therapy on the spectrum of other lesions or abnormalities that are part of the clinically-defined “diabetic retinopathy”. On the other hand, perhaps this can be explained by the possibility that pre-clinical researchers now are testing therapies that are closer to the actual molecular mechanism by which retinopathy can be inhibited than we were previously. An example of this is the strong research focus on anti-inflammatory approaches to inhibit the retinopathy, which is supported by the clearly beneficial effect on DME by corticosteroids in diabetic patients.

Very important insight has been provided recently by increasing evidence that essentially all retinal cell types become abnormal in diabetes, and that many of those cells participate in the development of diabetic retinopathy. For example, deletion of VEGF only from Muller cells markedly inhibits diabetes- induced abnormalities in retinal vascular function [78] and permeability [79]. Likewise, inhibiting phototransduction in photoreceptors [60,80] or slowing visual cycle activity by inhibiting RPE65 activity in retinal pigment epithelium [81] significantly inhibits the diabetes-induced increase in capillary leakage and degeneration. Even cells that are not part of the retina, such as leukocytes [82,83] and stem/progenitor cells [84] now are known to participate in the development of the vascular complications of diabetic retinopathy, or at least to fail to repair lesions that are developing due to diabetes. Evidence also suggests that multiple pathogenic processes are involved in the pathogenesis

of the retinopathy, and those signaling pathways can persist, converge, and change as glycemia fluctuates, and probably also change during different stages of the retinopathy.

Considering the myriad of different functions of those various cell-types and the different signaling pathways that are active in those different cells, the concept that the inhibition of a single pathway should be adequate to inhibit the development of the retinopathy seems much less promising than it once did. Proteomic and transcriptomic studies have indicated that single therapies administered to diabetic mice corrected only a fraction of the molecular defects in retina due to diabetes [85]. Thus, combinations of drugs that therapeutically modulate multiple mechanistic nodes within multiple cells or stabilize networks between different signaling pathways may enable better outcomes than treating with a single drug. Such approaches now are being tested for diabetic macular edema, but there is a strong rationale also for extending this to pre-clinical studies attempting to inhibit the earlier stages of the retinopathy [29].

Modern “-omic” profiling can enhance the pre-clinical development of therapies for the treatment of diabetic retinopathy or other diseases by providing a global assessment of the alterations in signaling systems caused by disease, and by providing a quantitative and unbiased assessment of how well a therapy returns that abnormal cell landscape to normal. The presumption of such an approach is that the therapies that best restore the transcriptome or other systems to normal are likely to be the best inhibitors of the retinopathy. Such an unbiased approach to therapy does not require prior knowledge (or bias) about which pathway or cell type(s) are involved or dominant in the progression of disease.

Animal models have provided tremendous insight into the pathogenesis of diabetic retinopathy to date, and are expected to continue to do so in the future, Nevertheless, there are steps that can be taken to make animal pre-clinical studies more relevant to clinical research and care, and thus, more useful.

One problem that impairs the clinical translation of results from animal studies of diabetic retinopathy (and other diseases) is that the endpoints used in the animal studies are not the same as those used in clinical studies. Thus, it has been difficult or impossible to verify that the effects of therapy in pre-clinical animal studies are (or are not) occurring also in similar clinical studies. For example, both clinicians and basic researchers agree that degeneration of retinal capillaries in diabetes is a powerful stimulus for retinal ischemia and eventual development of pre-retinal neovascularization. However, most animal studies evaluating the effect of a therapy on that retinal histopathology evaluate and quantitate the capillary degeneration microscopically at very high resolution after removal of the neural retina (“trypsin digest” method), whereas clinical evaluation of capillary degeneration in patients has been graded at low resolution using fluorescein angiography until now. New techniques are now available that can provide the same information in animals and in patients, and incorporation of optical coherence tomography (OCT), OCT-angiography (OCTA), 2-photon microscopy, and magnetic resonance imaging should allow direct comparison between the animal and patient studies using common techniques.

Another important difference between clinical and animal studies of diabetic retinopathy is that clinical studies place a priority on preserving or regaining vision in diabetes, but this has not been incorporated in many animal studies. Since there now is recognition that both vascular and neural abnormalities participate in the spectrum of abnormalities which make up diabetic retinopathy, animal studies need to measure both retinal histopathology and visual function, not one or the other. Finally, animal studies demonstrating reproducibility across different laboratories and in various species, multiple interventions targeting a common pathway yielding similar results and genetic data combined with therapeutic intervention all provide the best possibility of producing significant and reproducible results in humans.

Future animal studies also might follow-up on clinical observations that might provide novel insight into the pathogenesis of the retinopathy. For example, how does high myopia [86–88] inhibit the development of diabetic retinopathy? What are the mechanisms behind the development of diabetic-like retinopathy following radiation [89,90]?

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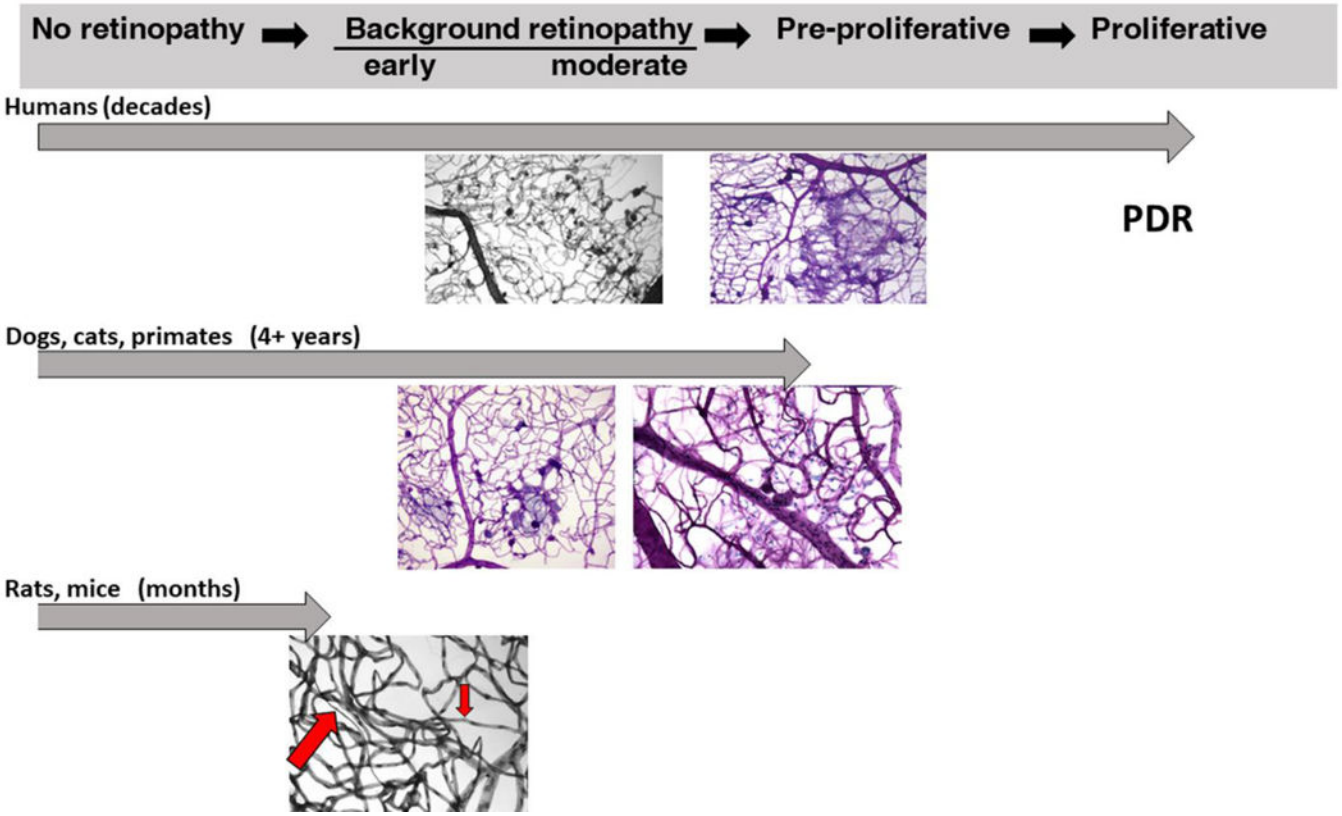

Fig 1.

Vascular histopathology of diabetic retinopathy progression is similar between species, differing mainly in the severity of the retinopathy that they develop (likely due at least in part to differences in life span). Diabetic patients can develop substantial microvascular pathology, including microaneurysms and degenerate capillaries, and in some cases, pre-retinal neovascularization. Similar lesions develop in large animal models of diabetic retinopathy, except that they have not been observed to develop pre-retinal neovascularization in the 5+ years of diabetes that they have been studied. Rodents develop predominantly only degenerate capillaries (large arrow) and pericyte ghosts (small arrow) and basement membrane thickening (not shown) in their limited lifetime. The duration of time needed for the various stages of the retinopathy in the different species are indicated in parentheses.