The microenvironment of diabetic retinopathy supports lymphatic neovascularization

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"We asked whether proliferative diabetic retinopathy involves the growth of new lymphatic vessels in addition to blood vessels – and, indeed, we found expression of lymphatic markers in the PDR tissues." The new study, conducted at the University of Helsinki, Finland, was published in the *Journal of Pathology*.

Proliferative diabetic retinopathy is a major sight-threatening diabetic complication. Nearly all patients with type I diabetes and over 60% of patients with type II diabetes develop retinopathy after 20 years of diabetes, despite metabolic control.

Proliferative diabetic retinopathy comes into existence through the process of pathological angiogenesis, when endothelial cells of the retinal vasculature invade their surroundings and project into the vitreous, the gel substance present inside the eye. The new vessels are fragile and leaky, which leads to vitreous haemorrhage and a fibrotic response that will eventually pull the retina causing retinal detachment and subsequent vision loss. When these vessels develop, diabetic patients are directed to vitreoretinal surgery whereby the newly formed pathological fibrovascular tissue is excised.

"Given the fact that current diabetic mouse models do not fully recapitulate this human diabetic eye complication, our research group set out to utilize these excised neo(fibro)vascular tissues for the in-depth

characterization of the disease pathophysiology," says researcher Erika Gucciardo from the University of Helsinki.

One major question the group had was to understand the nature of these vessels.

"Chronic tissue inflammation is present in proliferative diabetic retinopathy and we know it is connected with lymphangiogenesis. Therefore we asked whether proliferative diabetic retinopathy involves the growth or differentiation of new lymphatic vessels," Gucciardo explains.

The researchers found, indeed, expression of lymphatic markers in the PDR tissues.

"It is increasingly clear that studying the microenvironment is of fundamental importance to understand the mechanisms of a disease. The close collaboration between clinics and research laboratory opened such avenue," says Research Director Kaisa Lehti, Karolinska Institutet and University of Helsinki.

Vitreous samples were collected peri-operatively and used to understand the contribution of the diabetic intraocular microenvironment to the lymphatic endothelial involvement. The researchers found that indeed vitreous samples with increasing concentration of major lymphangiogenic growth factor VEGFC supported the lymphatic endothelial identity and corresponded to fibrovascular tissues with lymphatic marker expression.

The functionality of these vessels in PDR pathogenesis remains to be investigated. – It will be interesting to know whether these lymphatic vessels develop coincidentally with abnormal blood vessels or only later upon PDR progression and whether they are detrimental or beneficial,

e.g towards fluid removal and inflammatory cells trafficking, Gucciardo says.

All together these discoveries bring a new concept to diabetic microvascular complications and can lead to novel treatment approaches.

"In the future, therapeutic strategies targeting both lymphangiogenesis and angiogenesis may represent promising approaches for treating ischemia and inflammation-associated posterior segment retinal diseases, states ophthalmic surgeon," Dr. Sirpa Loukovaara from Helsinki University Hospital.

More information: Erika Gucciardo et al. Microenvironment of proliferative diabetic retinopathy supports lymphatic neovascularization, *The Journal of Pathology* (2018). DOI: 10.1002/path.5070

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