athens-NEPHROLOGY

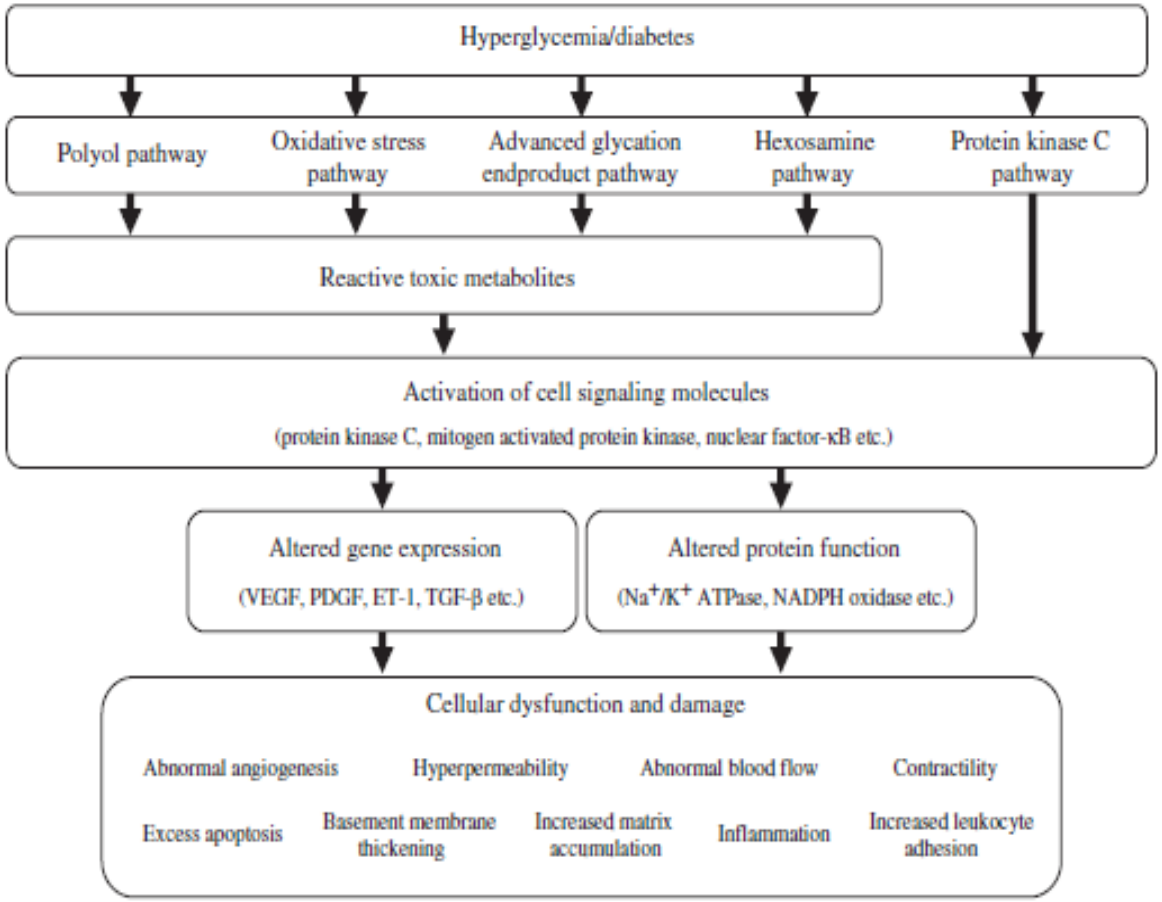
Ο αυξητικός ενδοθηλιακός παράγοντας των αγγείων και η Διαβητική Νεφροπάθεια

Ιωάννης Γ. Γριβέας, Νεφρολόγος, MD, PhD

Molecular mechanisms of diabetic vascular complications

Munehiro Kitada, Zhaoyun Zhang, Akira Mima, George L. King*

Journal of Diabetes Investigation Volume 1 Issue 3 June 2010



VEGF .... ????????

Vascular Endothelial Growth Factor

Originally described as endothelial **cell-specific mitogen** (Abraham and Schilling, 1989);
Now as VEGF and also known as **vascular permeability factor (VPF).**

VEGF is a sub-family of growth factors, to be specific, **the platelet-derived growth factor family of cystine-knot growth factors.**

Native VEGF is **a basic,** heparin-binding, homodimeric **glycoprotein of 45 kDa** (Ferrara, 1992).

Important signalling protein .

Mainly involved in **angiogenesis** and **vasculogenesis** .

Tumor cells , macrophages, platelets, keratinocytes, and renal mesangial cells etc .

VEGF plays a role in normal physiological functions such **as bone formation, hematopoiesis, wound healing, and development**. (Tischer and Vaisman 1990).

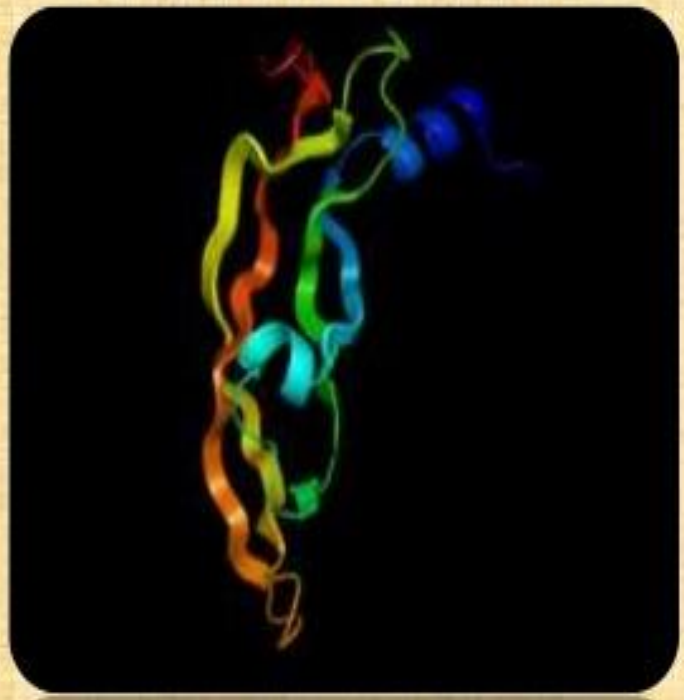
Classification of VEGF

Mammals – Five classes

- VEGF-A
- VEGF-B
- VEGF-C
- VEGF-D
- PGF

Viruses - VEGF-E

Snake venom - VEGF-F



Crystal structure of Vammin, a VEGF-F from a snake venom

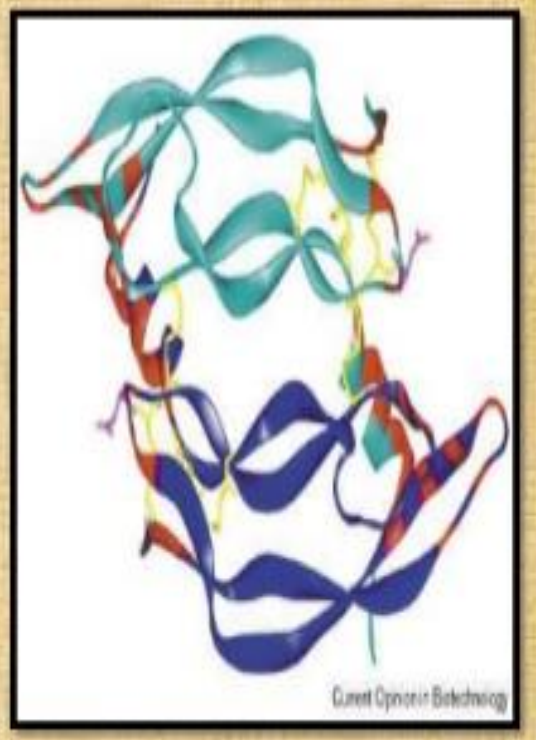
VEGF – A (Senger *et al.*, 1983)

Consist of **121, 165, 189** and **206** peptides in humans.

Main **isoforms**- 121 &165.

Found in chromosome **6** in **human** and **11** in **rats.**

Up regulate -**nitric oxide** production.

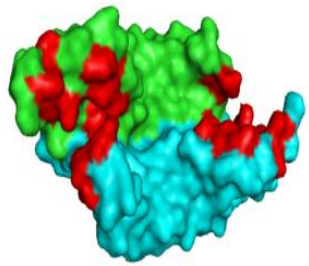


Oloffson et al., 2000

VEGF and the diabetic kidney: More than too much of a good thing

Syamantak Majumder, Andrew Advani *

Keenan Research Centre for Biomedical Science and Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada



Journal of Diabetes and Its Complications 31 (2017) 273–279

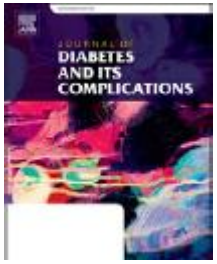
VEGF was "up" in diabetic rats and blockade of its actions attenuated albuminuria:
VEGF was "bad" in diabetic nephropathy.

Since that time, our understanding of the complex paracrine signaling cascades that are mediated by the VEGF family has expanded.
It has be come apparent that **it is not simply the amount of " VEGF"** that is important, but also

the type of VEGF,

the sites of VEGF action and the

context in which VEGF-mediated signaling occurs.



Am J Physiol Renal Physiol 296: F947–F956, 2009.
First published January 7, 2009; doi:10.1152/ajprenal.90601.2008.

Glomerular endothelial cell fenestrations: an integral component of the glomerular filtration barrier

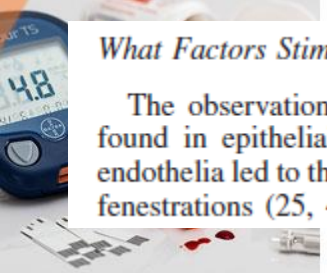
Simon C. Satchell[1] and Filip Braet[2]

[1]*Academic Renal Unit, University of Bristol, Southmead Hospital, Bristol, United Kingdom; and* [2]*Australian Key Centre for Microscopy and Microanalysis, The University of Sydney, New South Wales, Australia*

Table 1. ***Comparison of the three types of endothelial cell fenestrations***

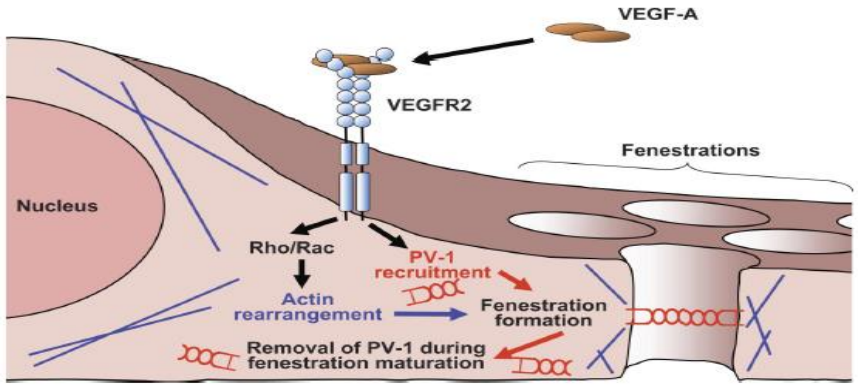
	Endothelium in Which Fenestrations are Expressed		
	Systemic capillaries, e.g.,gastrointestinal and renal peritubular	"Discontinuous" endothelium, e.g.,hepatic sinusoidal	Glomerular
Endothelial type	Fenestrated	Discontinuous	Fenestrated
Diaphragm	Yes	No	No
Diameter, nm	60–70	100–175	60–80
PV-1 expression	Yes	No (only in development)	No (only in development)
Cytoskeletal ring	?	Yes	?
Cholesterol ring	?	Yes	?
Basal lamina	Yes	No	Yes
Glycocalyx	Yes	?	Yes

PV-1, plasmalemmal vesicle-associated protein-1; ?, unknown.



What Factors Stimulate the Development of Fenestrations?

The observation that high levels of VEGF expression are found in epithelial cells closely associated with fenestrated endothelia led to the hypothesis that VEGF induces endothelial fenestrations (25, 44). This hypothesis has been investigated



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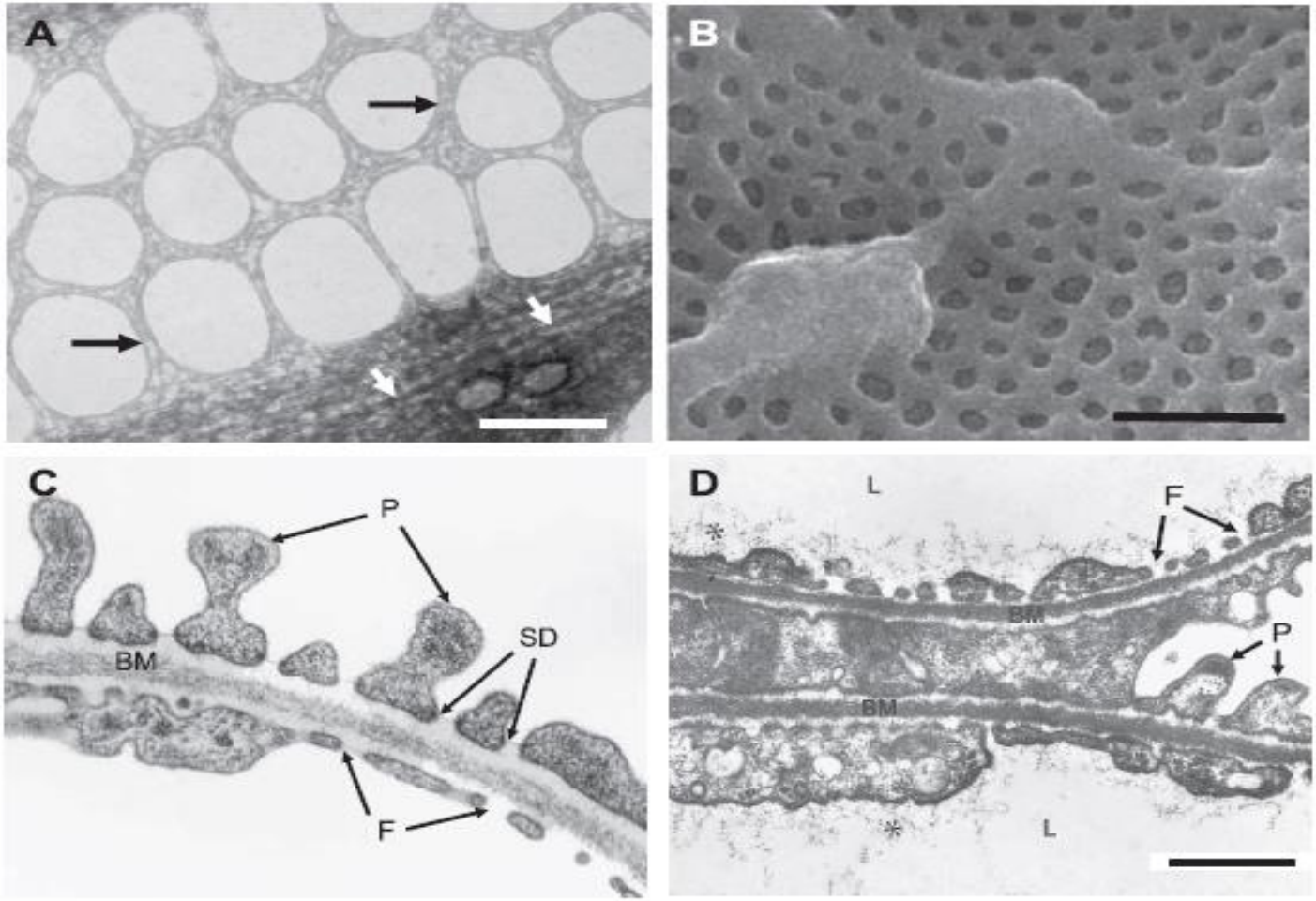

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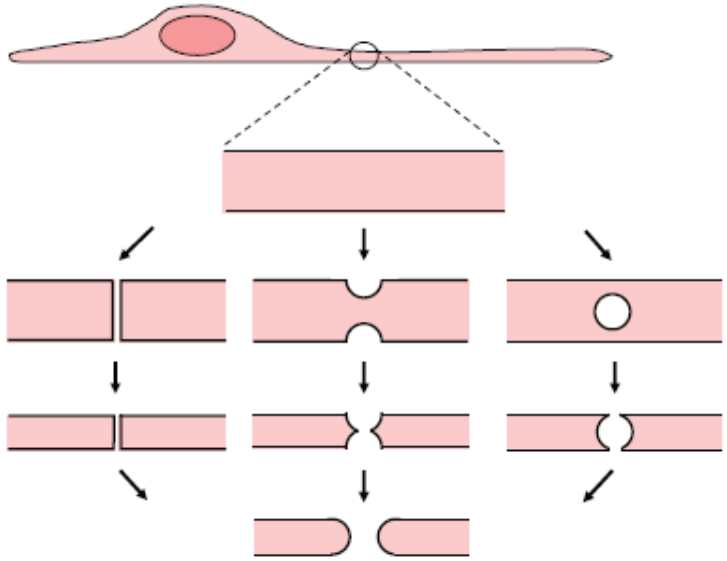

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Glomerular endothelial cell fenestrations: an integral component of the glomerular filtration barrier

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How are Fenestrations Maintained and Regulated?

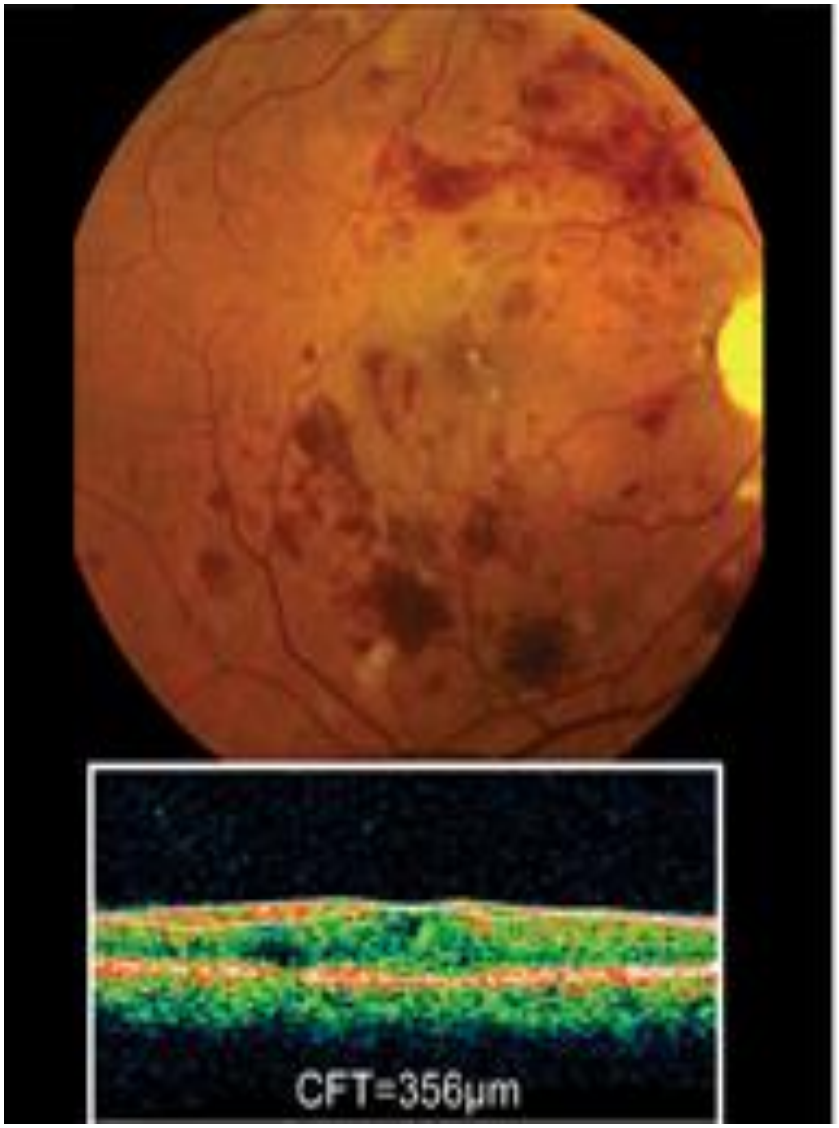
The above evidence points to a primary role for VEGF in maintenance of fenestrations as well as in their biogenesis. However, the question of whether GEnC fenestrations are dynamic structures is at present totally unexplored. The regres-

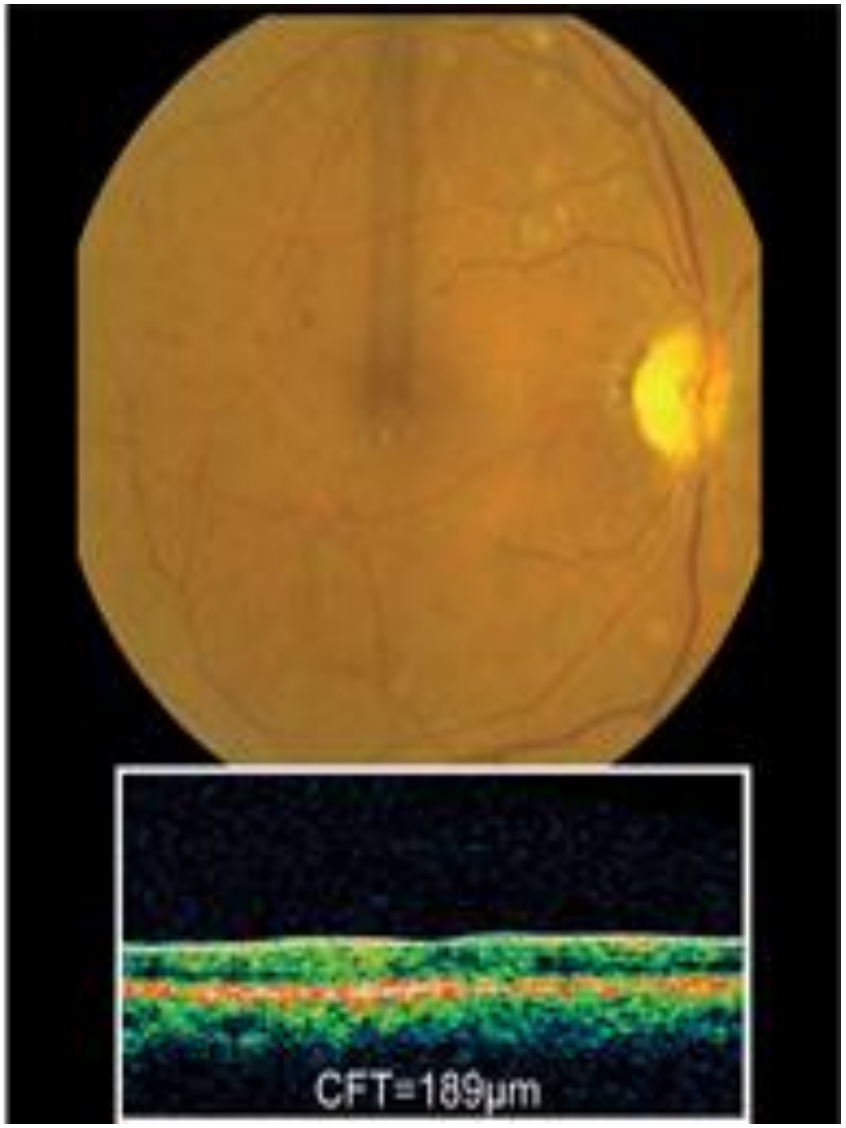
What is the Clinical Significance of GEnC Fenestration Dysfunction?

The reduction in GFR associated with loss of fenestral area predicted by biophysical models does indeed occur in preeclampsia where there is good evidence that this is the mechanism of acute renal failure (63). In this condition, increased circulating levels of soluble VEGFR1 bind to podocyte-produced VEGF and reduce availability for endothelial signaling (104). This results in endothelial thickening and a reduction in both size and density of fenestrations, "endotheliosis." GFR recovers as the condition resolves and fenestrations reappear.

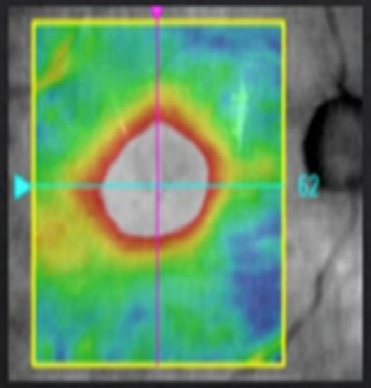
In a number of other instances, the glomerular endothelium is similarly damaged. These include both animal models [experimental diabetes (35, 46), uranyl nitrate-induced acute renal failure (6), cyclosporine nephropathy (62), serum sickness nephritis (33), and Thy-1 nephritis (55)] and human disease [diabetic nephropathy (107) and transplant glomerulopathy (112, 119)]. Although the impact of fenestral changes in these conditions has not been analyzed as carefully as in preeclampsia, it is inevitable that they contribute to the observed reduction in GFR in similar way. Neither the endothelium nor its

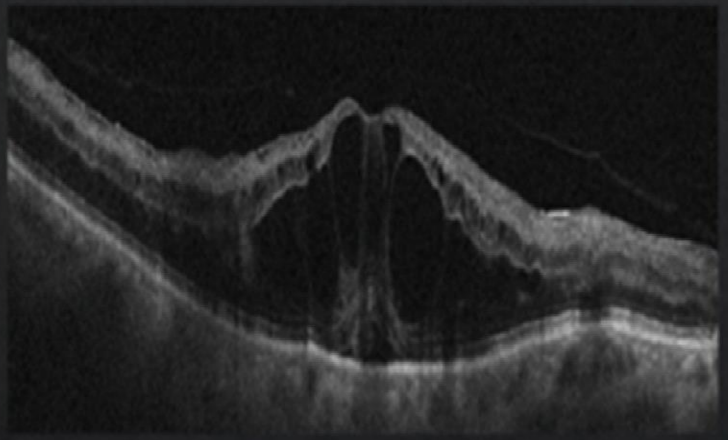

Contour TS
4.8

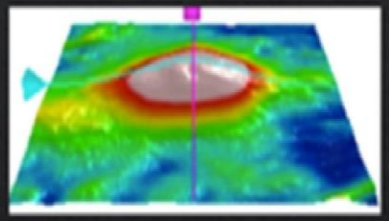

CFT=356µm


CFT=189µm

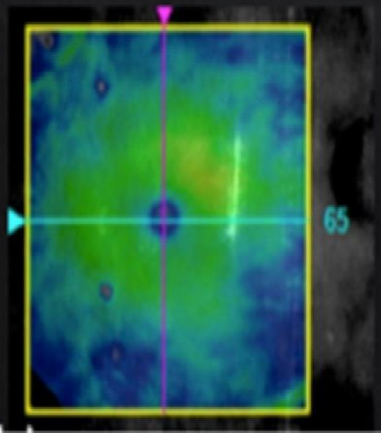
Pre ranibizumab

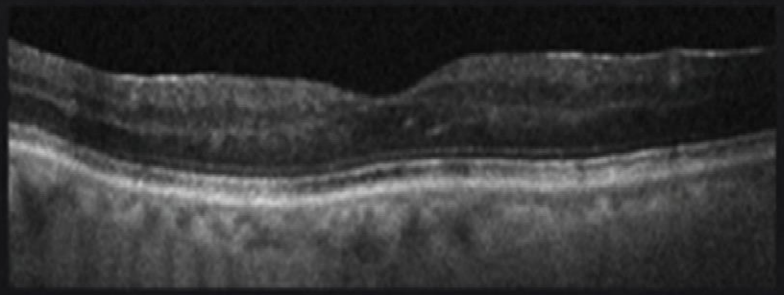


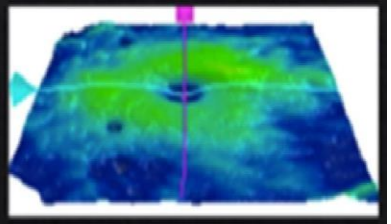




Post 2 aplicaciones ranibizumab







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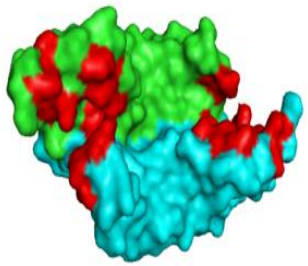

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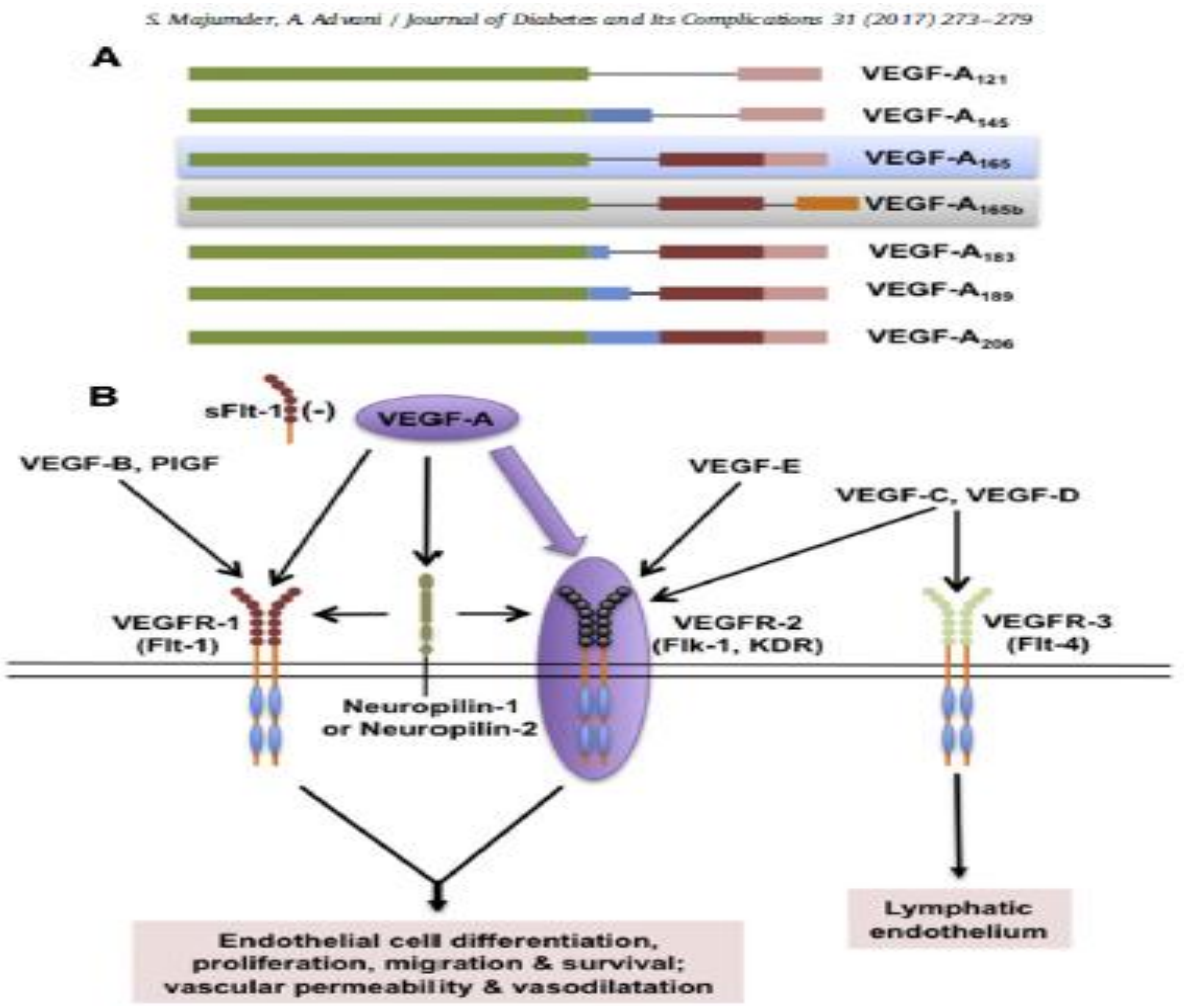
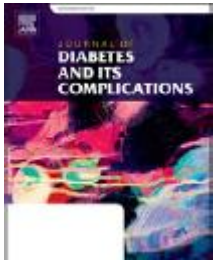
Journal of Diabetes and Its Complications 31 (2017) 273–279





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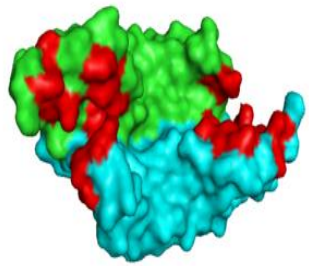

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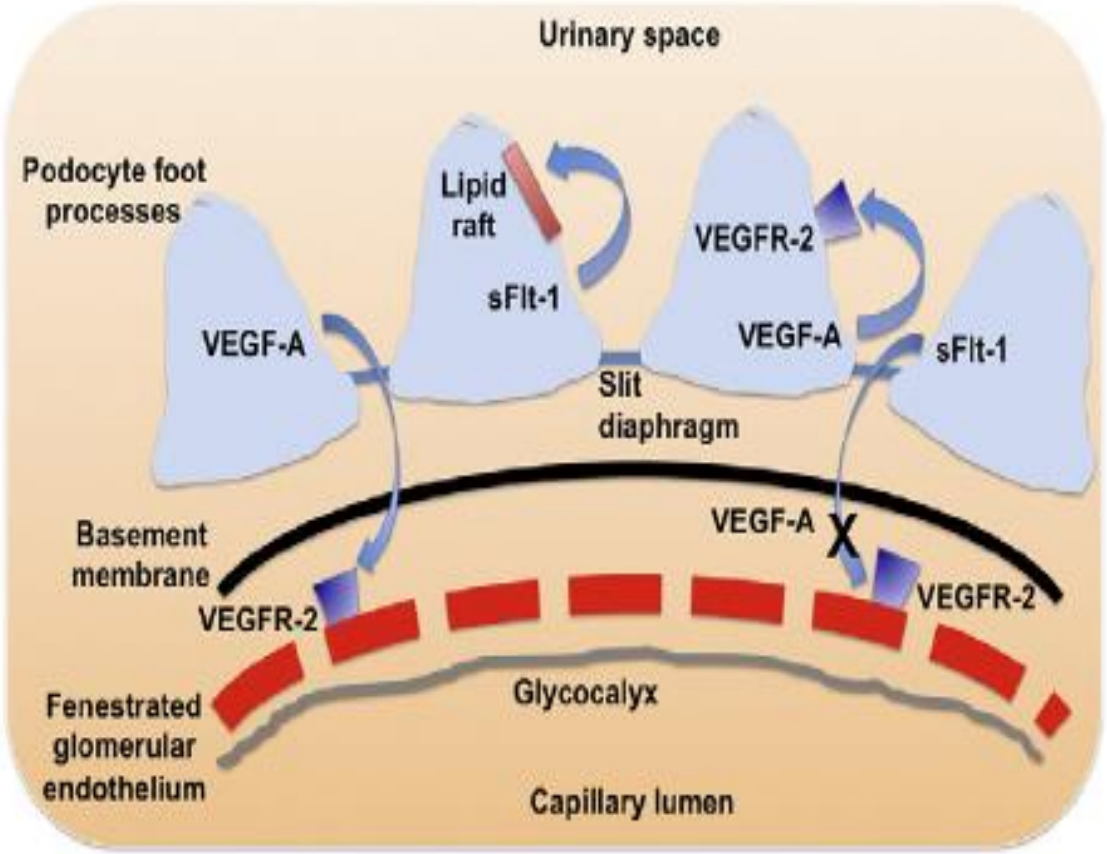

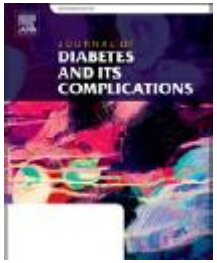

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Journal of Diabetes Investigation Volume 1 Issue 3 June 2010

Vascular Endothelial Growth Factor A

VEGF includes a family of growth factors that act on endothelial cells regulated by hypoxia and promote angiogenesis, increase permeability in vasculature, and is also known as a major regulator of endothelial proliferation, migration, and survival[144].

In early stage diabetic nephropathy, many reports have shown that the expression of VEGF-A is increased in glomeruli of diabetic animals[46,149,150] and proposed that inhibition of VEGF-A might have beneficial effects against diabetic renal injuries.

pole[154,155]. At the late stage of nephropathy, the expression of VEGF-A is decreased. Baelde *et al.* showed that the glomerular

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What is the physiological role of VEGF-A in the kidney, especially glomeruli? It is reported that treatment with anti-VEGF antibodies to patients with cancers[160] or within patients with preeclampasia[161] causes proteinuria and endothelial damage, suggesting that VEGF-A plays an important role in maintaining endothelial cell function and the glomerular filtration barrier. Supporting this, detailed reports by Quaggin *et al.* clearly show that VEGF-A is necessary for forming and maintaining the glomerular filtration barrier[162,163]. In their reports, using a condi-

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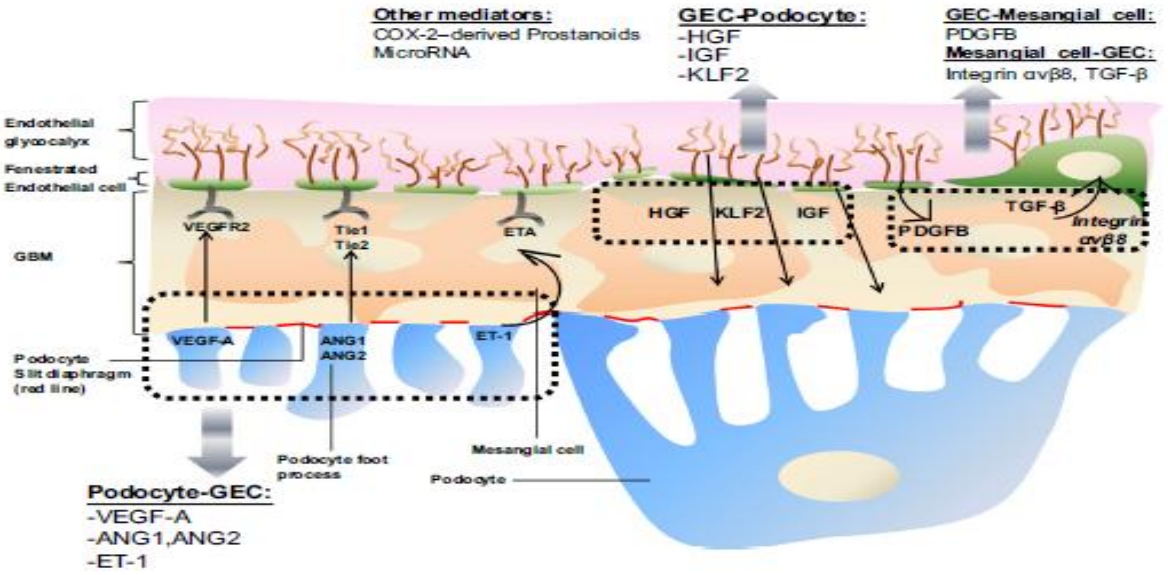
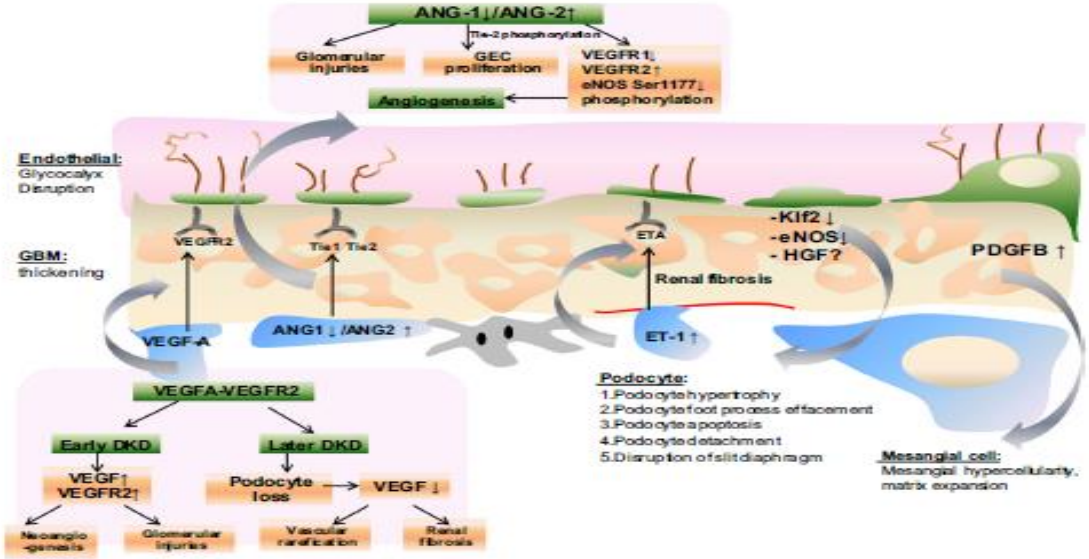
Is VEGF-A a bad or good player for the progression of diabetic nephropathy? Hohenstein *et al.* determined VEGF expression and its bioactivity in glomeruli of type 2 diabetic patients using specific antibodies for VEGF-A and VEGF-VEGFR complex[154]. Although VEGF expression of glomeruli is upregulated during all stages (mild, moderate and severe) of nephropathy, VEGF bioactivity in endothelial cells is only increased in mildly injured glomeruli and decreased in moderate or severe lesions. Furthermore, they showed that glomerular capillary rarefaction was linked to the degree of glomerulosclerosis and endothelial cell proliferation, showing capillary repair was markedly increased only in mildly/moderately injured glomeruli, even if apoptosis was detected in all stages. They suggest that diabetic nephropathy is associated with glomerular capillary rarefaction by an imbalance of endothelial cell proliferation, repair and apoptosis, and injury; and reduced VEGF activity might be an indicator of an insufficient capillary repair reaction[154]. Therefore, if increased VEGF expression occurs as a reaction of compensation for the damage of glomerular endothelial cells, inhibition of VEGF should not be given as a treatment for diabetic nephropathy. However, further studies are needed to conclude whether VEGF-A is or is not an endogenous protective factor for diabetic nephropathy.

A


Other mediators:
COX-2–derived Prostanoids
MicroRNA
GEC-Podocyte:
-HGF
-IGF
-KLF2
GEC-Mesangial cell:
PDGFB
Mesangial cell-GEC:
Integrin αvβ8, TGF-β
Endothelial glycocalyx
Fenestrated Endothelial cell
GBM
Podocyte Slit diaphragm (red line)
VEGFR2
Tie1 Tie2
ETA
HGF
KLF2
IGF
PDGFB
TGF-β
integrin αvβ8
VEGF-A
ANG1 ANG2
ET-1
Podocyte foot process
Mesangial cell
Podocyte
Podocyte-GEC:
-VEGF-A
-ANG1,ANG2
-ET-1

B


ANG-1↓/ANG-2↑
Tie-2 phosphorylation
Glomerular injuries
GEC proliferation
VEGFR1↓ VEGFR2↑ eNOS Ser1177↓ phosphorylation
Angiogenesis
Endothelial: Glycocalyx Disruption
GBM: thickening
VEGFR2
Tie1 Tie2
ETA
-Klf2↓
-eNOS↓
- HGF?
PDGFB ↑
Renal fibrosis
VEGF-A
ANG1↓/ANG2↑
ET-1↑
Podocyte:
1.Podocyte hypertrophy
2.Podocyte foot process effacement
3.Podocyte apoptosis
4.Podocyte detachment
5.Disruption of slit diaphragm
Mesangial cell:
Mesangial hypercellularity, matrix expansion
VEGFA-VEGFR2
Early DKD
Later DKD
VEGF↑ VEGFR2↑
Podocyte loss
VEGF↓
Neoangio-genesis
Glomerular injuries
Vascular rarefication
Renal fibrosis

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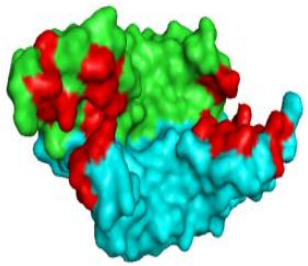

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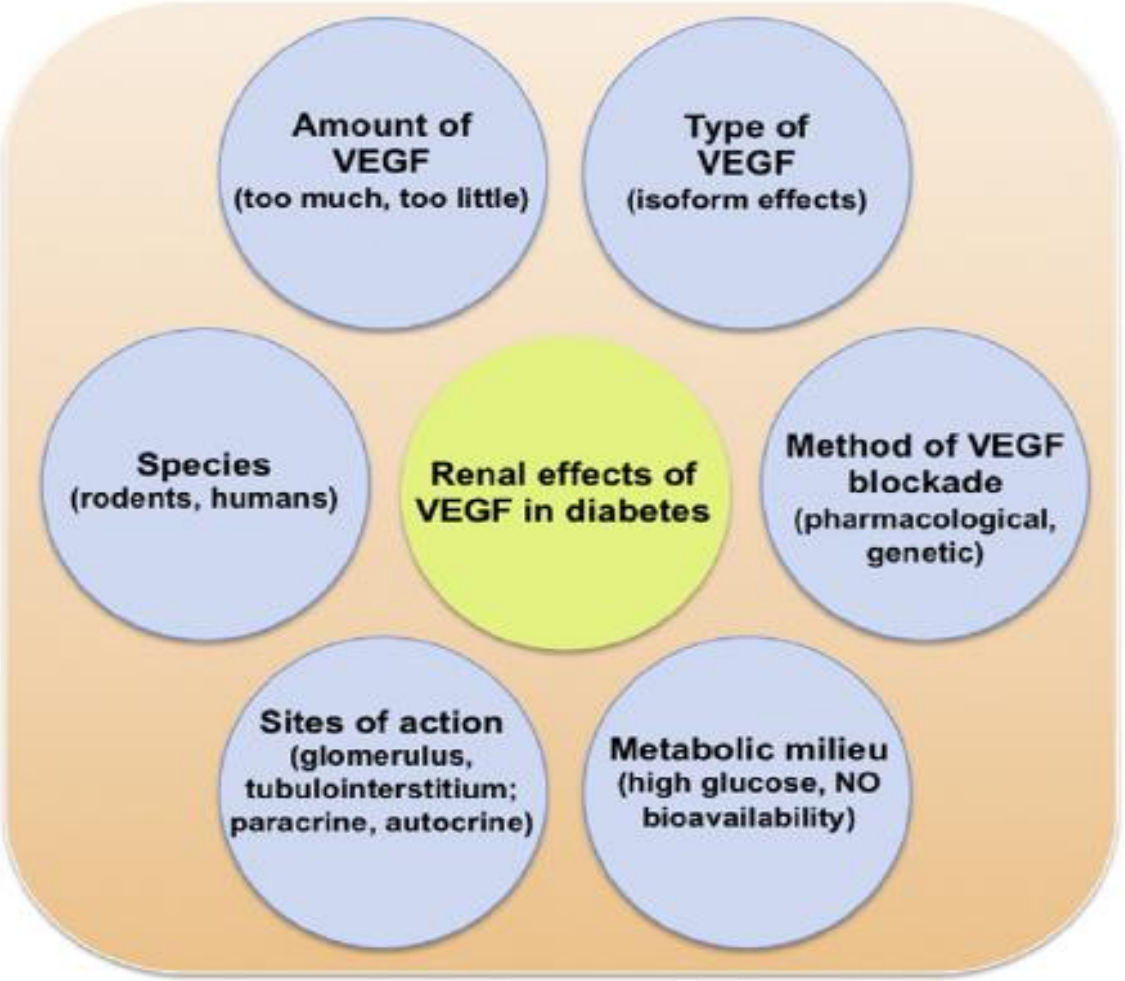

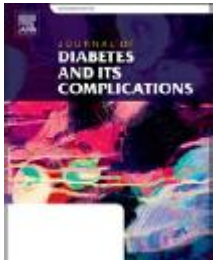

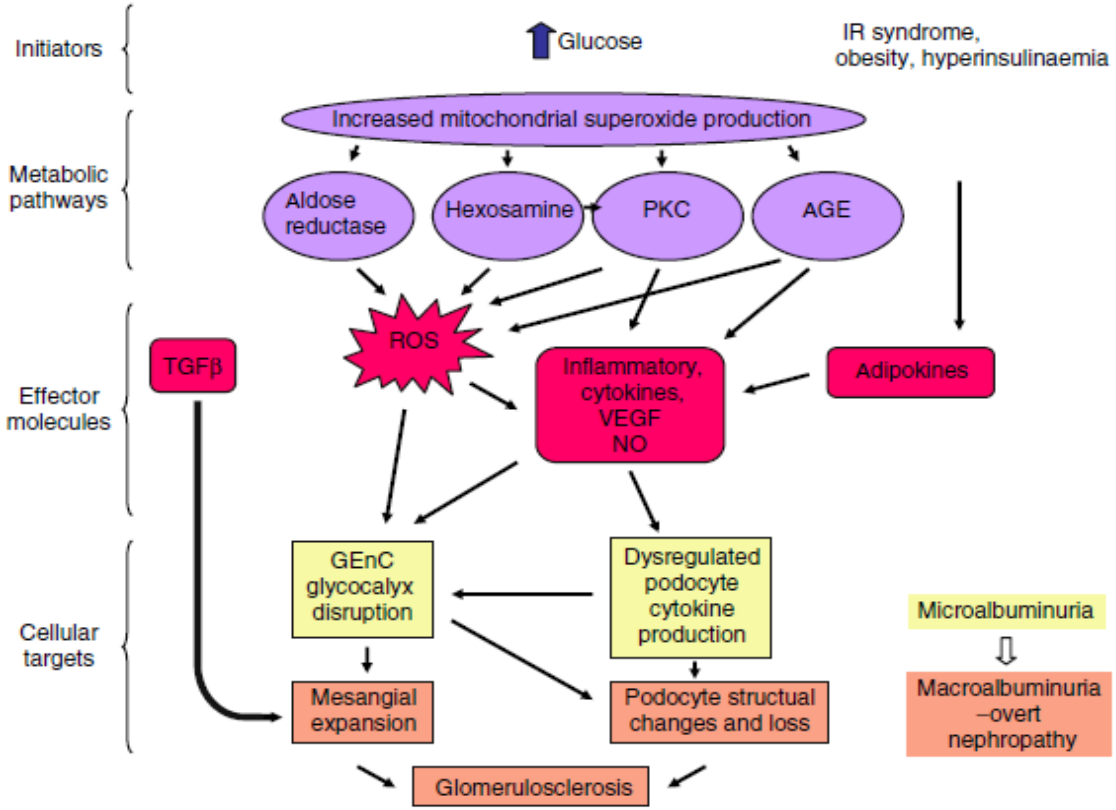

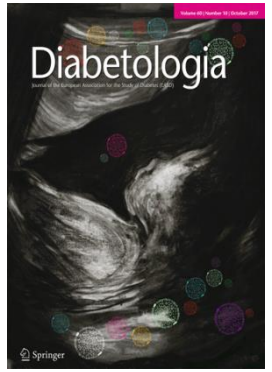

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DOI 10.1007/s00125-008-0961-8

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REVIEW

What is the mechanism of microalbuminuria in diabetes: a role for the glomerular endothelium?

S. C. Satchell · J. E. Tooke