The Glomerular Podocyte

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1. Introduction

Podocytes are glomerular epithelial cells with a neurone-like structure. They function to support the glomerular basement membrane so that efficient high volume filtration of blood under hydrostatic blood pressure can occur. Damage to or dysfunction of the podocyte population is associated with decreased filter efficiency and is manifest by movement of blood proteins across the filtration surface into the filtrate (proteinuria). It is now becoming clear that the podocyte has limited capacity to be replaced after injury. Thus podocyte loss from glomeruli ("podocytopenia") due to a number of different causes may be a key event leading to glomerular scarring (glomerulosclerosis) and resulting in End Stage RenaL Disease (ESRD).

2. An Overview of Podocyte Structure and Function

Each podocyte is an octopus-like structure whose processes interdigitate with those of its neighbors as together they support the delicate filtration surface (GBM) against the pulsating and ever-varying hydrostatic pressure of blood which is driving the filtration process. The podocyte cell body gives off primary processes from which secondary processes branch out in turn to give rise to tertiary ("foot") processes. Each foot process is attached to the foot process of a neighboring podocyte via a specialized adherens type junction (the filtration slit). The filtrate is formed by passage of fluid through the fenestrae of the inner endothelial cell, across the glomerular beasement membrane, and between foot processes. The "sole" of each foot process is attached to the underlying glomerular basement membrane by $\alpha 3\beta 1$ integrin probably via its interaction with laminin in the GBM. The space between podocyte processes is maintained by electrostatic negative charge repulsion as a result of a highly sialated glycocalyx consisting large part of the glycoprotein podocalyxin. The dynamic nature of this structure and its dependence on charge is emphasized by the finding that foot processes can disappear ("efface") within 10 minutes of injection of positively charged protamine into the ranal artery. The structure can be reconstituted within a further 10 minutes by injection of heparin to neutralize the protamine. Thus we have a picture of a highly specialized cell whose structure has evolved with the following features:

- the intercellular space between cells is maximized for the high volume formation of glomerular filtrate
- the intercellular adherens junction is modified for the function of filtration
- a very thin glomerular basement membrane is dynamically supported against the hydrostatic pulsatile pressure of blood which is driving the filter
- the filtration surface is supported at multiple sites through foot processes that al-

low the thin filtration surface (GBM) to work efficiently

- the highly selective characteristics of the filter are maintained by injection of special molecules from the podocyte and endothelial cell into the GBM

1. Podocyte Development
2. The Podocyte Cytoskeleton
3. Foot Process attachment to the GBM
4. Nephrin and the Filtration Structure
5. The Podocyte Glycocalyx
6. The Glomerular Basement Membrane
7. Oxidants and the Podocyte:
8. Transport of Macromolecules to the GBM
9. Podocyte Cell Division

Real and relative podocytopenia : Both experimental models and human biopsy materials suggest that relative lack of podocytes may be an important component of many glomerular diseases leading to focal and global glomerulosclerosis. This hypothesis is based on the concept that a podocyte is a non-dividing "post mitotic" cell. Each podocyte serves to maintain and support an area of the glomerular filter which it covers with foot processes, each foot process abutting those of a neighbor. The capacity of each podocyte to cover more area is limited. Therefore if podocytes are lost or the area to be served increases for any reason then regions of filter surface may lose their covering of podocyte foot processes. This loss triggers a series of events. This includes leakage of protein into the urine through the impaired and unmaintained filter surface and cellular responses to these events that may be understood as an attempt to minimize protein loss. Together these events lead to focal and global glomerulosclerosis.

Kritz and colleagues have provided the key experimental underpinning for the concept of podocyte function and insufficiency.

The most complete human data comes from Meyer and colleagues who have studied diabetes in the Pima Indian population. They provide compelling data to show that Pima Indians probably have fewer podocytes serving a larger glomerular surface area than do a control group made up of other ethnic origins. Progression of diabetes from micro-albuminuria to macro-albuminuria is associated with a further decriment in podocytes, particularly when factored for the increase in glomerular size and capillary surface area that occurs over this period. Thus the podocyte density (podocytes per glomerular volume measured as podocyte number/$10^6 \mu m^3$) goes from 235 ± 25 in the normal non-Pima population, to 89 ± 6 in early diabetic Pima, to 75 ± 3 in normo-albuminuric Diabetic Pima, to 70 ± 5 in micro-albuminuric Diabetic Pima and to 43 ± 3 in macro-albimunuric Diabetic Pima Indians. This depletion of podocytes is in contradistinction to other cells in the glomerulus which increase in number over this transition, although if corrected for increased glomerular volume the non-podocyte glomerular cell complement remains stable and is no different from that found in normal non-Pima glomeruli. Furthermore the degree of podocyte loss seems to predict the degree to which proteinuria increases when measured 4 years later ($r=0.57$), suggesting again that the number of podocytes has important prognostic impact. Since diabetic Pima Indians do not have hypertension as a major component of their clinical syndrome this confounding variable does not seem to be playing a major role in the sequence of events. Taken together these data strongly support a role for the podocyte in progression of diabetic glomerulosclerosis.