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COMMENTARY

Under the right conditions: protecting podocytes from diabetes-induced damage

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Abstract

Hyperglycemia-induced damage to the glomerular podocyte is thought to be a critical early event in diabetic nephropathy. Interventions that prevent podocyte damage or loss have been shown to have potential for the treatment of diabetic nephropathy. New data show that conditioned medium from adipocyte-derived mesenchymal stem cells has the potential to protect podocytes from high-glucose-induced damage. Furthermore, epidermal growth factor may be the critical ingredient mediating this effect. These data suggest that components of the conditioned medium of mesenchymal stem cells, in addition to the cells themselves, may have potential for the treatment of diseases such as diabetic nephropathy.

A new report from Li and colleagues has identified novel mechanisms by which glomerular podocytes may be protected during diabetic nephropathy (DN) [1]. DN is the leading cause of end-stage renal disease and is defined by pathological changes in the kidney causing progressive loss of the glomerular filtration rate, proteinuria and tubulointerstitial fibrosis [2]. Podocytes are terminally differentiated epithelial cells that form the filtration barrier with the glomerular endothelial cells. Under diabetic conditions, high glucose (HG) levels compromise the integrity of the glomerular filtration barrier via effacement of the podocyte foot processes and loss of podocytes from the glomerular basement membrane. This damage to the filtration barrier triggers a slow inexorable decline in renal function that can ultimately result in renal failure [3,4]. Currently available treatments can delay, but not prevent, the development of DN. The need to develop new therapies to target DN is thus essential.

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Mesenchymal stem cells (MSCs) are specialized progenitor cells that possess differentiation, proliferative and immunomodulatory potential. This, along with their ease of isolation, makes MSCs potentially an exciting new tool for regenerative medicine [5]. In this issue of *Stem Cell Research & Therapy*, Li and colleagues show that conditioned media of MSCs derived from human adipose tissue (hAD-MSCs) significantly reduced the apoptosis of HG-exposed podocytes. The key ingredient in this conditioned medium is suggested by the authors to be epidermal growth factor (EGF). Previous data from others suggested a potential beneficial effect of MSCs in the treatment of acute renal ischemia and DN [5,6]. hAD-MSCs injected into diabetic rats caused a reduction in DN severity without accumulation of MSCs within the kidneys [5]. This group therefore hypothesized that hAD-MSCs protected the kidney in a paracrine manner [5]. The potential of conditioned medium from hAD-MSCs to elicit a similar effect was assessed in the current study.

Li and colleagues used mouse podocyte clone 5 to elucidate the mechanism by which MSCs rescue HG-induced apoptosis of podocytes [1]. To establish a model of HG-induced podocytic apoptosis *in vitro*, the authors exposed the cells to normal glucose, normal glucose + mannitol, and HG for 24, 48 and 72 hours. An increase in podocyte apoptosis within the HG group at all time points was detected compared with the normal glucose and normal glucose + mannitol groups. This effect correlated with a decrease in the expression of podocyte proteins synaptopodin and nephrin within the HG group at all time points, suggesting that HG damaged the integrity of the glomerular filtration barrier.

Having established a model of HG-induced podocyte apoptosis, Li and colleagues next added MSC conditioned medium (MSC-CM) or human embryonic lung cell conditioned media (Wi38-CM) to the podocytes in all three treatment groups. The addition of MSC-CM decreased podocyte apoptosis and maintained the levels of synaptopodin and nephrin expression in the HG group.

The addition of Wi38-CM had no beneficial effect in this case. To understand why MSC-CM was more effective than Wi38-CM, Li and colleagues identified several cytokines that were present at higher levels in the MSC-CM compared with Wi38-CM. Of these, EGF was secreted in the greatest quantity. Given the previous reports of EGFs ability to repair and protect epithelial cells from apoptosis [7-9], the authors then treated podocytes exposed to HG with either MSC-CM or recombinant EGF. Flow analysis AnnexinV/Pi staining and western blot detection of caspase 3 confirmed the ability of EGF to inhibit HG-induced podocytic apoptosis. This effect was diminished when MSC-CM was co-incubated with a neutralizing antibody against EGF. This study clearly points to EGF as a key player within the MSC-CM in inhibiting HG-induced podocyte damage and apoptosis.

A particularly interesting aspect of this study is the demonstration that EGF plays a critical role in the restoration of the glomerular filtration barrier. EGF has been previously shown to promote the survival of epithelial cells of the intestine and kidney [7,9]. In contrast to the current study, others have shown a pathogenic role for the EGF receptor in DN [10] and progressive glomerulonephritis [11]. The current study clearly shows a cytoprotective role of EGF on podocytes exposed to HG. Further study is required to fully elucidate the disparity around the role of EGF in kidney disease, and also to more fully define the protective mechanism triggered by the conditioned medium from hAd-MSCs for podocytes during DN.

The work here augments seminal work done by others and identifies a tantalizing new possibility whereby injecting MSCs themselves for the treatment of DN (and indeed other diseases) may not be necessary. Rather, harvesting and injection of the conditioned medium from these cells may be sufficient to harness the potential needed to regenerate and repair damaged glomerular filtration membrane. Future work is needed to define the full potential of this novel cell-free treatment modality for DN.

Abbreviations

DN: Diabetic nephropathy; EGF: Epidermal growth factor; hAD-MSC: Mesenchymal stem cell derived from human adipose tissue; HG: High glucose; MSC: Mesenchymal stem cell; MSC-CM: Mesenchymal stem cell conditioned medium; Wi38-CM: Human embryonic lung cell conditioned media.

Competing interests

The authors declare that they have no competing interests.

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