Mechanisms of glomerular crescent formation

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INTRODUCTION — The presence of crescents in glomeruli is a histologic marker of severe injury. In general, the severity of the renal failure and other clinical manifestations of glomerulonephritis (eg, hypertension, edema) correlates with the percentage of glomeruli that exhibit crescents [1-5]. In addition, the duration and potential reversibility of the underlying disease correspond with the relative predominance of cellular or fibrous components in the crescent (show histology 1A-1E).

Although crescentic GN is most commonly found in the syndrome of rapidly progressive GN (RPGN), these lesions may occur in glomeruli in most forms of inflammatory glomerular injury. These include post-infectious GN, IgA nephropathy, systemic lupus erythematosus, renal vasculitis, and membranoproliferative glomerulonephritis (MPGN).

This topic will review the mechanisms of crescent formation in the glomerulus. The mechanisms and pathogenesis of glomerular damage in glomerulonephritis are presented separately. (See "Mechanisms of immune injury of the glomerulus" and see "Pathogenesis of damage in glomerulonephritis").

INITIATING EVENTS — The initiating event in all glomerular crescents is the development of a physical gap, or hole, in the glomerular capillary wall and glomerular basement membrane (GBM) (show histology 2) [6]. Similar gaps in Bowman's capsule also correlate with crescent formation [7,8]. These lesions are presumably mediated by processes primarily involving macrophages and cell-mediated immunity. (See "Mechanisms of immune injury of the glomerulus").

When such a disruption to the integrity of the glomerular capillary occurs, circulating
cells, inflammatory mediators, and plasma proteins pass through the capillary wall and into Bowman's space. Similarly, rents in Bowman's capsule allow cells and mediators from the interstitium to enter Bowman's space, and for contents of Bowman's space to enter the interstitium, contributing to periglomerular inflammation. The development of a crescent subsequently results from the participation of coagulation factors, particularly fibrin, tissue factor, and several different proliferating cell types, including the macrophage, the parietal glomerular epithelial cell, and the interstitial fibroblast.

FORMATION AND COMPOSITION — Crescents are conventionally defined as the presence of two or more layers of cells in Bowman's space. The major participants are coagulation proteins, macrophages, T cells, fibroblasts, and parietal epithelial cells. Podocytes are being increasingly recognized as contributors to crescent formation.

Coagulation proteins — Central to most forms of crescent formation is the presence in Bowman's space of coagulation factors which lead to the cross-linking of fibrin, and deficiency in fibrinolytic mechanisms in Bowman's space may facilitate the development of a fibrin clot. The importance of fibrin is illustrated by the finding that defibrination completely prevents crescent formation [9,10]. Tissue factor, tissue factor inhibitor and plasminogen/plasmin system are pro-coagulant molecules that are central to this process:

Tissue factor — The primary stimulation for fibrin deposition appears to be tissue factor, a 31 kD protein that binds to and activates factor VII [11]. This protein is derived from endothelial cells, podocytes, and macrophages [11,12]. Macrophage derived interleukin-1 and tumor necrosis factor also stimulate its production by glomerular endothelial cells [13]. In early GN, tissue factor expression appears to derive from resident glomerular cells; later, it principally originates from macrophages [11].

Tissue factor inhibitor — Accompanying the increase in tissue factor activity is an early reduction in tissue factor pathway inhibitor (TFPI), thereby favoring fibrin deposition [14]. Administration of recombinant TFPI significantly reduces fibrin deposition and crescent formation [14]. This early response is followed by the enhancement of TFPI expression in later stage disease, chronically inhibiting the deposition of fibrin [15].

Plasminogen/ plasmin system — The plasminogen/plasmin system is central to
fibrinolysis and resolution of crescents. In experimental GN, for example, there is decreased fibrinolytic activity due to decreased plasminogen activator (tPA), and increased plasminogen activator inhibitor (PAI-1) [11,16]. The end result is that extraglomerular fibrin cross-linking occurs in Bowman's space. Fibrin is a potent chemotactic factor that also helps recruit macrophages into glomeruli [17].

Macrophages — Macrophages are central to the formation of crescents, as both tissue factor expression and fibrin deposition are macrophage-dependent phenomena [18]. Macrophages presumably derive from the circulation, and also probably enter from the periglomerular interstitium via gaps in Bowman's capsule. These gaps may be caused by inflammatory processes similar to those that result in rupture of GBM [7,8], or they may represent cell-mediated lesions [19,20].

Localization of macrophages to the glomeruli involves multiple chemoattractants, including fibrin, macrophage chemoattractant protein-1 (MCP-1), macrophage inhibitory factor (MIF), macrophage inflammatory protein-1-alpha (MIP-1-alpha) and osteopontin [21-24], and adhesion molecules, such as VCAM-1, ICAM-1, and CD44, which are all expressed on parietal epithelial cells [25,26]. The expression of the receptor for MCP-1, chemokine receptor 2B (CCR2B), may be particularly important in localizing macrophages to glomeruli [27]. Renal cell derived granulocyte-macrophage colony stimulating factor (GM-CSF) may increase expression of VCAM, MCP-1, and IL-1 beta, thereby influencing crescent formation [28]. (See "Leukocyte-endothelial adhesion in the pathogenesis of inflammation").

Once localized to Bowman's space, activated macrophages contribute to crescents by proliferating, and by releasing the following molecules. Other procoagulant factors. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) [29,30]. These two cytokines upregulate adhesion molecule expression, stimulate cell proliferation, and recruit more macrophages [29]. Selective blockade of IL-1 with IL-1 receptor antagonists, and of TNF with soluble TNF receptors markedly reduces crescent formation [30-32]. In contrast to the macrophage origin of most inflammatory mediators, some evidence suggests that the principle source of TNF may be intrinsic renal cells [33]. Transforming growth factor (TGF) beta is a potent stimulus for the production of collagen I and probably mediates in part the transition from cellular to fibrocellular and fibrous crescents [34]. In an animal model of glomerulonephritis, administration of a chimeric soluble TGF receptor ameliorated extracellular matrix formation [35]. In a small study of patients with
crescentic glomerulonephritis, those with higher urinary TGF-beta levels were less likely to respond to immunosuppressive therapy, possibly reflecting more severe disease [36].

T cells — T cells are found in Bowman's space and in crescents [19,37]. Localization of T helper cells to the glomeruli may involve traditional chemoattractants (such as MCP-1 and MIP-1alpha), certain cytokines (such as IL-12p40 and IL18), mast cells and costimulatory ligands on macrophages and non-lymphoid cells (such as CD80 and CD86) [38-40]. Some of these cytokines may also stimulate production of proinflammatory cytokines such as interferon gamma and TNF [38]. The principal role of T cells in glomerular injury may be antigen recognition and macrophage recruitment (via the release of factors such as MIF and interferon-gamma) [41,42].

The role of T cells does not appear to be prominent. Although maneuvers such as T cell depletion, blocking MIF, and deleting the interferon-gamma gene substantially reduce crescent formation, this finding probably reflects a reduction in the severity of intracapillary (and perhaps periglomerular) macrophage-mediated injury and not any direct role for the T cell.

Fibroblasts — In some examples of crescentic GN, the second most prominent cell type is the interstitial fibroblast [7,8]. These cells are believed to enter Bowman's space from the periglomerular interstitium through gaps in Bowman's capsule. In the crescent, the fibroblast is a major source of interstitial (or type I) collagen which characterizes the transition from cellular to fibrous crescents. Fibroblast proliferation is likely growth factor-dependent, probably involving basic fibroblast growth factor (bFGF) [17,43].

Parietal epithelial cells — Although macrophages are an important cell type in glomerular crescents, parietal epithelial cells are also significant constituents [44]. Unlike visceral glomerular epithelial cells (GEC), or podocytes, which are terminally differentiated cells with little proliferative capacity, the parietal epithelial cells can and do proliferate, presumably in response to growth factors, such as platelet derived growth factor (PDGF) and bFGF [17]; proliferation of parietal epithelial cells may be facilitated by reduced expression of cyclin kinase inhibitors [45]. Since the parietal epithelial cells are not major sources of procoagulant molecules or growth factors, it is unlikely that they are as important as macrophages and fibroblasts in determining the course and consequences of crescent formation. However, they may be the principal cells
producing type I collagen [46].

Podocytes — Podocytes (visceral glomerular epithelial cells), considered to be terminally differentiated cells, had not been regarded as participants in crescent formation. However, podocytes may undergo epithelial mesenchymal transformation to contribute to crescents, particularly in early crescent formation [47-49].

RESOLUTION OF CRESCENT FORMATION — The presence of crescents does not portend irreversible glomerular damage. In IgA nephropathy, for example, most glomeruli may exhibit cellular crescents during episodes of gross hematuria, yet the lesion can resolve with little or no scarring [45]. This lack of progression occurs when the crescents are predominantly cellular, without a significant fibroblast or collagen component. (See "Causes and diagnosis of IgA nephropathy").

Whether crescents progress or resolve may depend upon the integrity of Bowman's capsule and the resulting cellular composition of the crescent. Production of interstitial collagen and progression to fibrous crescents is more common when capsular rupture occurs and fibroblasts along with macrophages are prominent in Bowman's space [17]. Although the presence of fibrous crescents generally correlates with glomerular sclerosis, there is no good evidence that the events in the crescents cause injury to the glomerular capillaries themselves. As an example, defibrination abolishes crescent formation without improving renal function [9,10]. Rather, crescent formation appears to be a consequence of capillary injury. However, there is increasing evidence that large crescents may occlude the outlet from Bowman's capsule to the proximal tubule to produce "atubular glomeruli" with subsequent degeneration of both glomeruli and tubules [50].

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