Mesenchymal Stem Cells in Acute Kidney Injury

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Abstract
The potential role of mesenchymal stem cells (MSCs, also called mesenchymal stromal cells) in endogenous repair and cell-based therapies for acute kidney injury (AKI) is under intensive investigation. Preclinical studies indicate that administered MSCs both ameliorate renal injury and accelerate repair. These versatile cells home to sites of injury, where they modulate the repair process. The mechanisms responsible for their protective and regenerative effects are incompletely understood. Some have reported that MSCs are capable of direct engraftment into injured nephrons under certain circumstances. This is highly controversial, however, and even those who argue there is engraftment acknowledge that the primary means of repair by these cells most likely involves paracrine and endocrine effects, including mitogenic, antiapoptotic, anti-inflammatory, and angiogenic influences. There is a good deal of interest in MSC-based approaches for the treatment of human kidney injury, thanks to positive preclinical results, the strong clinical need for novel therapies to treat AKI, the ease of isolation and expansion of MSCs, and encouraging preliminary clinical trial results in other fields. This review summarizes current knowledge and identifies gaps in our understanding of MSC biology that will need to be filled in order to translate recent discoveries into therapies for AKI in humans.
INTRODUCTION

Stem cells play fundamental roles in the self-renewal of adult tissues throughout life. Some tissues are characterized by ongoing loss of cells, including the hematopoietic system, intestine, and skin, and adult stem cells are responsible for replenishing these cells to maintain tissue homeostasis. Other organs, such as kidney and lung, have a much lower rate of cellular turnover but are capable of proliferating and repairing after an injury (1). Some injured tissues can be reconstituted by the recruitment, proliferation, and differentiation of epithelial stem cells, but it remains unclear if the kidney follows this paradigm for epithelial stem cell–based homeostasis and repair after injury (2). Basal tubule cell turnover in kidney is exceedingly low, and the turnover that can be detected appears to occur by division of terminally differentiated tubular epithelial cells (3). Soon after injury, by contrast, there is diffuse tubular cell proliferation. This may reflect the intrinsic ability of surviving epithelial cells to adapt to the loss of neighboring cells by dedifferentiation and proliferation, and ultimate replacement of the cells that have died as a result of the insult (Figure 1). Based on the high proliferative capacity of injured kidney, one longstanding model holds that tubular cells themselves are the source of nephron repair (1).

Studies on the role of bone marrow–derived cells (BMDCs) have challenged this model of dedifferentiation followed by proliferation and redifferentiation of existing tubular cells after injury. Bone marrow (BM) contains at least two populations of stem cells: the hematopoietic stem cells (HSCs), which give rise to all differentiated blood cell types, and mesenchymal stromal cells (MSCs), which give rise to mesenchymal cell types including chondrocytes, osteocytes, and adipocytes. Although it has long been appreciated that BM-derived inflammatory cells home to injured kidney, recent studies have suggested that BMDCs directly participate in renal injury and repair. Mesenchymal stem cells in particular have been reported to protect against experimental renal injury as well as accelerate the repair process in rodent models. Some reports (reviewed below) indicate that MSCs directly replace dead tubular epithelial cells, whereas other observations suggest that MSCs regulate the endogenous reparative machinery without transdifferentiation into tubular cells. Overall, the emerging evidence describing MSC modulation of acute kidney injury (AKI) has stimulated a reappraisal of the cellular mechanisms behind renal injury and repair and has generated considerable excitement about the prospects for novel cell therapies to treat human kidney diseases.

THE MESENCHYMAL STEM CELL

MSCs are undifferentiated adult cells that can be isolated from a variety of tissues but primarily BM stroma. The embryonic lineage of these cells is mesodermal; they emerge from mesenchymal cells that give rise to connective tissues such as bone, cartilage, and fat.
Transdifferentiation: a switch in the fate of a cell, usually a differentiated cell, into a different differentiated cell type

Acute kidney injury (AKI): clinical syndrome characterized by a rapid fall in glomerular filtration rate, often due to ischemic or toxic renal injury. Previously known as acute renal failure as well as blood supply–related organs such as the vasculature and hematopoietic system.

MSCs are defined by adherence to plastic in culture, multipotentiality (ability to differentiate into different cell types), expression of typical surface markers such as CD73, CD90, and CD105, and the absence of expression of hematopoietic lineage markers (4). MSCs reside not only in BM but also in fat and vasculature and may be present in all adult tissues, including kidney (5). There is no proof that MSCs are clonal, self-renewing stem cells, and for this reason, many define MSCs as “multipotent mesenchymal stromal cells” (6).

The functional properties of MSCs make them unique. These multipotent stem cells can differentiate to cells of the mesenchymal lineage such as osteocytes, adipocytes, and chondrocytes, and potentially other cell types. Directed differentiation can be achieved by culturing MSCs in defined conditions (7). MSCs are easily cultured, unlike embryonic stem cells (which require feeder cells and special growth medium) and other adult stem cells. Because MSCs can be expanded, it is not difficult to obtain clinically useful numbers of cells so they have been among the first cells to be used for cellular therapies in humans. Finally, MSCs possess immunomodulatory properties that make them especially attractive for potential use in treating human disease characterized by autoimmunity or inflammation, including graft-versus-host disease, multiple sclerosis, and Crohn’s disease (8).

BONE MARROW PLASTICITY AND RENAL REPAIR

The current interest in MSCs for treatment of AKI grew in part from the observations that BM-derived cells could develop into hepatocytes (9, 10). This finding, later reported in humans (11), led to intensive research on the plasticity of BM-derived cells. Evidence for engraftment of BM-derived cells was soon reported in other tissues, including lung, gastrointestinal tract, and skin. Krause et al. demonstrated that a single transplanted HSC could provide hematopoietic reconstitution for a lethally irradiated recipient and that this single hematopoietic cell could also engraft nonhematopoietic tissues including lung, liver, gastrointestinal tract, and skin (12). These surprising results were followed by studies of renal biopsies from male patients transplanted with female kidneys. Two groups reported the presence in the allografts of Y-chromosome-positive tubular epithelial cells—varying from <1% up to 20% of cells examined (13, 14), with similar results found in mice (15).

Follow-up studies have led to a reevaluation of the physiologic relevance of the initial observations concerning BM-derived cells transdifferentiating into renal epithelia. It has been proposed that the early results could be due to cell fusion or possible artificial detection of lineage markers. The inability to repeat some of these findings in other labs has also raised doubts (16, 17). Not all issues are resolved but several conclusions are possible. The method of marking and detecting the BM lineage is critical. Bacterial β-galactosidase transgene activity may be problematic owing to high expression of endogenous kidney β-galactosidases and possible leakage of the enzyme by damaged cells, with subsequent uptake by neighboring cells. Green fluorescent lineage markers, such as enhanced green fluorescent protein, are also subject to misleading artifacts because of the high intrinsic autofluorescence of the posts ischemic kidney. High-resolution marker detection in kidney sections is especially important; three-dimensional deconvolution or confocal microscopic techniques are required to distinguish true cellular staining from closely apposed and overlying cells and nuclei (18). BM-derived leukocytes traffic to the renal interstitium after renal injury, and a superimposed leukocyte nucleus may be mistaken for an epithelial cell nucleus without sufficiently high-resolution imaging. Cell overlay and intrinsic autofluorescence have
also complicated interpretation of BMDCs’ contribution to myocardial regeneration. It is difficult to track cell fate in vivo, particularly in injured tissues (19, 20).

Recent studies of mice with BM transplants harboring several different lineage markers have indicated that BM-derived cells only rarely contribute to the renal epithelial lineage under physiologic conditions (at most 0.1% but probably less) (21, 22, 27). The importance of cell fusion as a possible explanation for earlier results is emphasized by a recent study that convincingly showed a 20%–50% fusion of tubular epithelia with BM-derived cells in a mouse model characterized by long-term, intense genetic pressure (23). Clearly the mechanism and relative importance of cell fusion under normal conditions require further study.

**MSCs AMELIORATE RENAL INJURY AND ACCELERATE REPAIR**

Although we conclude that endogenous BM-derived cells or exogenously administered MSCs do not directly replace renal epithelia to a significant extent during renal repair, several lines of evidence indicate that exogenously administered MSCs do modulate the kidney repair and regenerative response. Intravenous injection of the lineage-negative BM fraction prior to injury, part of which contains MSCs, blunts the initial rise in BUN after ischemia reperfusion injury (IRI) (24), whereas whole BM has no protective effect (21). Injection of purified MSCs almost completely protects against the cisplatin-induced rise in BUN, whereas injection of purified HSCs has virtually no protective effect (25). Similar protection from injected MSCs was found in a glycerol-induced pigment nephropathy model (26) and in a model of IRI (22, 27). Importantly, infused MSCs have been shown to enhance recovery of rodents subjected to IRI even if administered 24 h after the injury, suggesting active participation of these cells in the repair process (27, 28, 52). Taken together, there is good evidence that administered MSCs protect against AKI and accelerate the recovery phase in toxic and ischemic rodent models.

**DO EXOGENOUS MSCs DIRECTLY ENGRAFT INTO INJURED TUBULES?**

Morigi et al. (25) and Herrera et al. (26) reported that exogenous MSCs can engraft into injured tubules and proposed that the ability to transdifferentiate explained their protective effect. Yokoo et al. directly injected exogenous MSCs into developing kidney and after subsequent embryo and organ culture observed MSC incorporation into glomerulus, tubule, and interstitium, findings that seem to support the possibility of direct engraftment (29). In contrast, other studies (18, 21, 22, 27) showed protection from injury by exogenous MSCs but very little or no tubular incorporation. Some of the discord may be explained by different injury models and protocols (30); however, the caveats described previously regarding proof of tubular incorporation of BMDCs also apply to studies of injected MSCs. The nature of the MSC marker, careful three-dimensional microscopic analysis, and the possibility of cell fusion all must be taken into account. In a follow-up study, Herrera et al. (31) reported much lower tubular incorporation of MSCs (∼2.5%) than in an earlier report (∼20%) that had relied on the same glycerol-induced renal injury model but a different fluorescence-based method of tracking injected MSCs.

In our opinion, the data indicate that the effects on renal repair of exogenous MSCs are not explained by direct repopulation of the tubule. The timing of renal epithelial cell proliferation seems too rapid to be explained by transdifferentiation of extrarenal cell types into epithelial cells. In most studies, the protective effect of injected MSCs is observed within 24–48 h. When careful lineage analysis has been done, the numbers of MSC- or
BMDC-derived epithelial cells appear to be so low (0.1% or less) that they could not have functionally contributed to repairing the nephron, at least by direct engraftment. Vogtsseder and colleagues have argued that in the uninjured kidney, the small amount of epithelial proliferation present occurs by division of terminally differentiated cells (3, 32). Lin et al. have presented preliminary evidence that at least a subset of genetically tagged tubular epithelial cells proliferate after injury (33). Both observations suggest that reparative cells in renal injury derive from within the kidney.

In summary, there is a growing consensus that both endogenous BMDCs and exogenously administered MSCs can give rise to renal epithelial cells only rarely, if at all, and that cell fusion may explain some of the results interpreted as direct replacement of epithelial cells. The rarity of transdifferentiation to kidney epithelia indicates that direct tubule repopulation by BMDCs or administered MSCs does not have physiologic relevance to renal repair from injury in vivo.

HOMING OF EXOGENOUS MSCs

The mechanisms by which MSCs promote kidney repair remain unclear, but an important aspect of the therapeutic effects of MSCs is their apparent ability to home to injured organs. After exogenous MSCs labeled with iron-dextran were administered to rats following IRI, magnetic resonance imaging located these cells primarily in the renal cortex. These cells remained associated with kidney three days after IRI, and histologically they were localized to glomerular capillaries (28). In a more detailed analysis, fluorescently labeled MSCs were localized by two-photon microscopy to both glomeruli and peritubular capillaries within 10 min of intra-arterial injection into rats subjected to IRI 24 h before (27). The relative importance of MSC homing to glomerular versus peritubular capillaries is not known. MSCs have been detected in both compartments in both acute and chronic injury models (34). Either location may be efficacious, with peritubular MSCs poised to signal to adjacent tubular epithelia and glomerular MSCs potentially able to secrete factors that are filtered into the tubular lumen, where they may bind to and directly regulate and/or facilitate proliferation of damaged epithelial cells. Another unresolved question is whether MSCs bound to the renal microvasculature are capable of migrating into the renal interstitium. No direct evidence supports this possibility, but it has not yet been examined rigorously.

Recent studies have begun to dissect the signals that regulate MSC homing. An attractive candidate has been the chemokine SDF-1 (stromal-derived factor-1), which binds to its receptor CXCR4, which is expressed in distal tubule, and is upregulated after renal injury (35). CXCR4 is expressed in MSCs. Its expression is upregulated by hypoxia, and the SDF-1/CXCR4 pair is known to regulate HSC migration. Furthermore, hypoxic preincubation of MSCs appears to increase engraftment in vivo (36). Another promising candidate as a regulator of homing is platelet-derived growth factor (PDGF), a growth factor known to be secreted from the basolateral aspect of human epithelial cells (37). Cultured MSCs express PDGF receptors and potently migrate in response to exogenous PDGF. This migratory response is enhanced by preincubation of MSCs with tumor necrosis factor (TNF) (38). A recently described candidate for regulation of MSC homing is CD44, which is expressed on MSCs and required for renal localization of injected MSCs after glycerol-induced renal injury. The receptor for CD44, hyaluronic acid, is upregulated in kidney after injury, and CD44-negative MSCs show reduced migration to injured kidney as well as decreased protection from injury (31). Elucidating the precise mechanisms controlling MSC migration to injured kidney may have important clinical consequences, since effective delivery of these cells to damaged tissue may be critical for therapeutic efficacy.
Evidence That MSCs Repair Kidney by Paracrine and Endocrine Mechanisms

If MSCs do not directly repopulate repairing tubules, then paracrine and/or endocrine mechanisms must explain their therapeutic effects in kidney injury. Given the importance of inflammation in the pathophysiology of acute kidney injury (39), it is very important to consider the immunomodulatory properties of MSCs and the role these may play in renoprotection (40). MSCs are immunologically privileged, and allogeneic MSCs do not induce a proliferative T cell response. The mechanisms for this tolerance include low surface expression of both major histocompatibility complex (MHC) class I and II molecules, lack of expression of major costimulatory molecules such as CD40, CD80, and CD86, and direct inhibition of dendritic cell alloantigen-induced differentiation and activation, among others (41). MSCs also exert anti-inflammatory influences on T cells. Co-culture of MSCs with either Th1, Th2, or natural killer (NK) cells decreases their secretion of proinflammatory cytokines such as TNF-α and IFN-γ and increases their secretion of suppressive and tolerance-promoting cytokines such as IL-10; this effect is largely mediated by MSC production of the eicosanoid prostaglandin E2 (PGE2) (42). T cells are important in both immune-mediated and ischemic kidney disease, so the ability of MSCs to regulate T cell function is probably relevant to their therapeutic effects in AKI (43).

Studies have begun to address the specific paracrine factors secreted by MSCs that might explain their beneficial effects in AKI. Togel et al. (51) found significant levels of VEGF, HGF and IGF-1 in MSC-conditioned media, which was capable of enhancing endothelial cell proliferation and differentiation. When MSCs were infused just prior to IRI, these cells quickly homed to the renal microvasculature, and endogenous cell apoptosis was decreased in regions that contained MSCs. These authors propose that the ability of MSCs to home to injured microvasculature and inhibit apoptosis is an important aspect of MSC-induced renoprotection (51). Whether the therapeutic effects of MSCs can
Figure 2
Mechanisms of immunomodulation by MSCs. The immune suppressive effects of MSCs may be amplified after exposure to proinflammatory stimuli such as TNF-α or IFN-γ. Although NK cells can lyse MSCs by activating lectin NKG2D ligands expressed on MSCs, pre-exposure to IFN-γ protects MSCs from cytolysis, and MSCs inhibit IL-2-induced NK cell proliferation. After proinflammatory stimuli, MSCs process soluble antigen and present it to CD4+ T cells. Soluble factors are very important in mediating anti-inflammatory effects of MSCs. PGE2, nitric oxide, HGF, IL-10, TGF-β, and IDO all exert inhibitory effects on immune cells in a paracrine fashion. Adapted from Reference 40 with permission.

be entirely ascribed to their ability to home to injured tissues and secrete trophic mediators, i.e., to deliver growth factors, is an important open question. Some doubt about the importance of tissue homing has been raised by a recent report in which the intraperitoneal injection of MSCs also conferred protection from IRI in the absence of MSC trafficking to kidneys (52). Whether the higher local concentrations of paracrine factors released from intrarenal MSCs versus lower systemic concentrations released from extrarenal MSCs are critical factors in their therapeutic effect requires careful follow-up studies.

Figure 3 summarizes the paracrine mechanisms for the therapeutic effects of MSCs in AKI.

RECRUITMENT OF ENDOGENOUS BONE MARROW MSCs
The observation that exogenously administered MSCs can protect against renal injury naturally leads to the question of whether endogenous MSCs might be recruited to participate in the repair process as well. It has been hypothesized that endogenous BM-derived MSCs may circulate in much the same fashion as HSCs, and some studies have reported that MSC-like cells can be purified from blood, albeit in very low numbers (53). Whether endogenous MSCs may be recruited from their BM niche and home to sites of injury is an unresolved issue. Although it is very clear that BM-derived cells, primarily inflammatory cells, traffic to the interstitium of injured kidney, it is unknown whether a subset of these cells comprises MSCs. Genetic lineage analysis in chimeric mice has proven that BMDCs traffic to the interstitium of injured kidney (22, 54), but whether these interstitial BMDCs include MSCs has not been ascertained to date (55). It is worth noting that the proportion of MSCs compared to non-MSCs in whole BM is very low (0.01% or less), so it is very likely that the great majority of BM-derived cells in injured kidney are
inflammatory cells such as monocytes, macrophages, neutrophils, and lymphocytes.

**KIDNEY MSCs**

An alternative possibility to homing of BM-derived MSCs is activation of an endogenous kidney MSC population. Gupta et al. (56) isolated a population of cells from adult rodent kidney that expressed markers of MSCs (CD90, CD44), expressed Oct4 but not cytokeratin, self-renewed in culture, and incorporated into the renal epithelium. The authors called these cells multipotent renal...
progenitor cells and suggested that they were candidate renal stem cells. Bussolati et al. (57) isolated a CD133+ population from human kidney and found CD133+ cells in the interstitium and within tubular cells. These cells did not express hematopoietic markers but expressed MSC markers (CD29, CD90, CD44, and CD73). When these cells in Matrigel were injected subcutaneously into SCID mice, they developed into tubular structures that expressed proximal and distal tubular markers. When cultured in vitro with VEGF, they expressed endothelial markers, and when these differentiated cells were injected subcutaneously in Matrigel, they were reported to form vessels that connected to the endogenous mouse vessels. When injected into mice with glycerol-induced AKI, these cells homed to the kidney and reportedly integrated into proximal and distal tubules.

Sagrinati and coworkers isolated a population of CD133+CD24+ parietal epithelial cells from human adult kidney that could be induced in vitro to express markers of proximal and distal tubular cells, osteogenic cells, adipocytes, and neurons (58). Finally, Plotkin & Goligorsky (5) isolated a multipotent clonal cell line from kidney and showed that these cells could differentiate into erythropoietin-producing fibroblasts in hypoxic culture. These cells migrated to a peritubular and interstitial location, but not a tubular location, after injection into postischemic kidney. Although it is not yet clear what type of cells each group has isolated, one interpretation of these intriguing studies is that kidney-specific MSCs exist. Whether these cells participate in repair of injured kidney, either indirectly or through direct epithelial engraftment, requires further study. It is also possible that kidney MSCs may contribute to some of the adverse longer term effects of injury, such as interstitial fibrosis through activation of fibroblasts and/or differentiation into fibroblasts.

**THE NEXT STEP: CLINICAL TRIALS FOR MSCs IN ACUTE KIDNEY INJURY?**

BM-derived cell therapies for several human diseases are already being tested. Most attempts have been made in the field of myocardial infarction, where several small phase I and phase II trials have reported modest improvements in both physiologic and anatomic parameters after intracoronary delivery of various populations of BMDCs, including MSCs (59). Calls for large randomized trials of cell therapies are now being made (60), and the first phase I trial of MSCs in AKI is scheduled to begin shortly. This safety study will enroll cardiac surgical patients at high risk for developing AKI. Patients who are scheduled to undergo on-pump coronary artery bypass grafting or valve surgery and who possess renal risk factors such as pre-existing renal disease, diabetes, age >60 years, and redo surgery will be enrolled. Because autologous MSCs will need to be expanded in vitro, most surgeries will be elective, but one arm of the study will involve the administration of allogeneic MSCs to patients in need of emergent surgery (C. Westenfelder, personal communication). An important advance has been the storage of well-characterized human MSCs by Prockop’s group at Tulane University, where banked MSCs are available to investigators (http://www.som.tulane.edu/gene_therapy/distribute.shtml). With the development of biomarkers for earlier detection of AKI (61), it is possible that we can one day identify patients at an early stage of AKI, select matched MSCs, thaw them, and infuse within 24 h of the renal insult.

MSCs have had a very good safety record in human studies to date. Unlike pluripotent embryonic stem cells, MSCs do not form teratomas in animals when injected in vivo. In the human trials reported so far, no major adverse effect has been attributed to the injection of this cell type. Nevertheless, little
long-term follow-up information about the consequences of administered MSCs is available. In a recent study, Kunter et al. (34) injected MSCs intrarenally into rats in a model of glomerulonephritis. Although there was a beneficial therapeutic effect, on day 60 ~20% of the glomeruli of MSC-treated rats contained large adipocytes derived from maldevelopment of MSCs with pronounced surrounding fibrosis. Ectopic osteogenic maldevelopment of MSCs has also been observed in a cardiac cryoablation injury model (62). One possible explanation for the observations of Kunter and colleagues is the high number of MSCs injected. These investigators injected $2 \times 10^6$ MSCs into the renal artery of rats, whereas Westenfelder and others have injected $1 \times 10^5$ cells into the suprarenal aorta of mice. Even after normalization for kidney size, Kunter et al. injected significantly more MSCs, and the resulting high local cellular concentration may predispose toward certain pathways of MSC differentiation.

AMNIOTIC FLUID–DERIVED STEM CELLS

Multipotent stem cells isolated from amniocentesis specimens—termed amniotic fluid–derived stem cells (AFSs)—hold promise for use in cellular therapy (63). AFSs represent ~1% of all amniotic fluid cells and are characterized by expression of the cell surface marker c-kit, as well as other surface antigens also expressed by MSCs (e.g., CD73, CD90, CD105). Like MSCs, and unlike embryonic stem cells, they do not form teratomas in vivo. AFSs differ from MSCs in two important ways. First, they are significantly more broadly multipotent than MSCs and may in fact be pluripotent. Second, they are clonal, and therefore are a true stem cell population. Whether these properties of AFSs will make them a better candidate for cellular therapies in kidney injury needs to be investigated. Their accessibility makes them a very attractive candidate for regenerative medicine. The prospect of banking amniocentesis specimens for future AFS isolation and use in autologous cell therapies, or matching histocompatible donor cells with recipients, represents an important potential advance in regenerative medicine.

SUMMARY POINTS

1. Kidney epithelial cells show very high proliferation after acute injury but very low proliferation in the basal state.
2. Bone marrow (BM)-derived cells can incorporate into repairing renal epithelium, but these events are rare, may be explained by cell fusion, and are not the primary physiologic mechanism for nephron regeneration.
3. MSCs are multipotent cells derived from BM and perhaps in the adult kidney itself. They are easily expanded in BM culture, facilitating their use in cell therapies.
4. MSCs are capable of homing to injured kidney when injected intravenously soon after injury.
5. MSCs can accelerate functional repair of injured nephrons, most likely through paracrine and endocrine mechanisms. The physiologic significance and long-term consequences of transdifferentiation and/or fusion with epithelial cells are unclear.

FUTURE ISSUES

1. What molecular signals regulate homing of MSCs to injured tissues?
2. Do endogenous MSCs exist in the kidney and, if so, how do they participate in repair and longer-term complications of injury such as fibrosis?
3. If MSCs accelerate repair primarily through paracrine mechanisms, which secreted factors underlie these effects?

4. Do endogenous MSCs circulate, and can they be mobilized pharmacologically to accelerate kidney repair?

5. Do other stem cell types (such as amniotic fluid–derived stem cells; see sidebar) or kidney-specific MSCs possess similar repair capabilities?

6. Are there long-term risks, such as maldifferentiation or transformation, associated with administered MSCs?

DISCLOSURE STATEMENT
The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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