but also clarify and disseminate information on best practices, and ensure that the health-care system has the capacity to meet the evolving needs of patients once they are identified. We must have reliable tests that accurately discern at-risk populations, evidence-based strategies that truly decrease the occurrence of adverse outcomes in these patients, and the ability to implement these strategies effectively. The findings of Stevens and his colleagues[5] will help to inform the discussion surrounding CKD identification and management — particularly as further data on outcomes from this and similar initiatives become available in the future.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Tumor necrosis factor-α in cisplatin nephrotoxicity: A homebred foe?

Z Dong[1] and SS Atherton[1]

A robust inflammatory response involving tumor necrosis factor-α (TNF-α) is induced during cisplatin nephrotoxicity. Using chimeric models, Reeves and colleagues now demonstrate that resident kidney cells, rather than infiltrating immune cells, are the major producers of TNF-α. Blockade of TNF-α attenuates inflammation and associated kidney injury.

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Cisplatin, a widely used chemotherapeutic agent, is used to treat a variety of cancers. A major drawback of this drug is its side effects in normal cells and tissues, prominently toxicity in the kidneys. Over 30% of patients develop renal problems during cisplatin treatment, which limits the use and efficacy of cisplatin in cancer therapy. The cellular and molecular mechanism of cisplatin nephrotoxicity is a topic of intense investigation, is very complex, and involves multiple factors and processes, including a robust inflammatory response and, ultimately, death of renal tubular cells.[1]

Tumor necrosis factor-α (TNF-α) is a key player in the inflammatory response during cisplatin nephrotoxicity. TNF-α production was induced under the pathological condition.[2–4] Importantly, in TNF-α-deficient mice, the production and secretion of proinflammatory cytokines and chemokines were attenuated, and this was associated with amelioration of acute kidney injury and renal failure during cisplatin treatment. Similar observations were shown for TNF-α inhibition by pharmacological inhibitors and neutralizing antibodies.[3] Together, these studies have demonstrated a critical role for TNF-α in mounting the inflammatory response during cisplatin nephrotoxicity and the ensuing kidney tissue damage and acute renal failure.

Given the role of TNF-α in cisplatin nephrotoxicity, several important questions remain. How does cisplatin induce TNF-α expression? Where is TNF-α produced and by what cells? How does TNF-α stimulate the proinflammatory response? By what mechanism does TNF-α induce kidney injury and renal failure? Reeves and colleagues[5] (this issue) have now provided significant insights into these important questions. Specifically, they have demonstrated that resident cells of the kidneys, rather than infiltrating inflammatory cells, are the major contributors of TNF-α production during cisplatin nephrotoxicity.[5]

When considering cytokine and chemokine production under pathological conditions, many of us tend to think about an origin from cells of the immune system. However, in the kidney, there are a variety of cells that can efficiently produce and secrete cytokines and chemokines. For example, production of TNF-α has been shown in mesangial cells, glomerular cells, endothelial cells, and renal tubular cells. So, is TNF-α produced by infiltrating immune cells or parenchymal cells of the kidneys? To address this question, Reeves and

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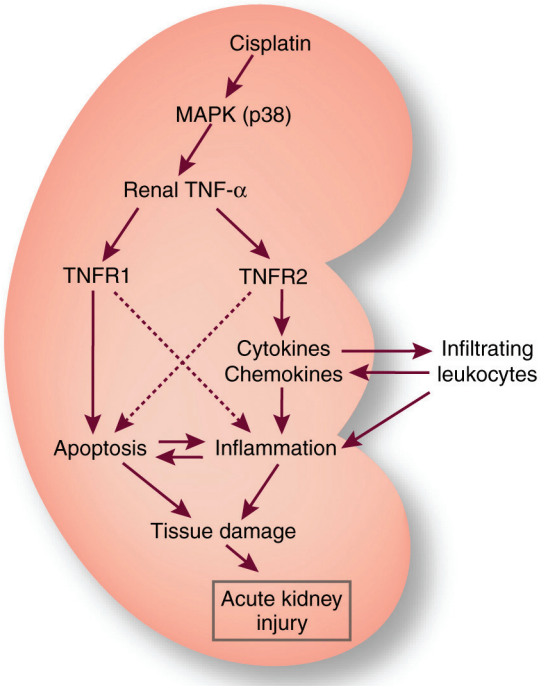

Figure 1 | Schematic diagram depicting TNF-α production and involvement in cisplatin-induced acute kidney injury. MAPK, mitogen-activated protein kinase; TNFR, TNF-α receptor.

colleagues[5] created chimeric models in which bone marrow of recipient animals was ablated and then reconstituted with bone marrow derived from wild-type (WT) or TNF knockout (KO) donor mice. The reconstitution led to four types of chimeric mice (donor bone marrow genotype → recipient genotype): WT→WT, KO→WT, WT→KO, and KO→KO. After cisplatin treatment, the WT recipients (WT→WT and KO→WT) maintained their capacity for TNF-α production, whether WT or TNF-α KO bone marrow was reconstituted. In sharp contrast, TNF-α production was diminished in the TNF-α-deficient recipients, regardless of WT or KO bone marrow reconstitution. Thus, cisplatin-induced TNF-α production in the chimeric models was determined by the genetic background of the recipient and not by the donor bone marrow. These are remarkable findings, which suggest strongly that TNF-α is produced locally by resident cells of the kidneys, rather than by bone marrow-derived immune cells that infiltrate the organ during cisplatin nephrotoxicity. Notably, WT→WT and KO→WT chimeras developed severe kidney injury and renal failure after cisplatin treatment, whereas WT→KO and KO→KO chimeras did not. This observation, although not surprising or particularly novel in view of the demonstrated involvement of TNF-α in cisplatin nephrotoxicity, indicates that TNF-α produced by the kidneys has an important pathogenic role.

In addition to having an elegant experimental design involving chimeric models, the study by Reeves and colleagues[5] was also very carefully controlled. By transplantation of green fluorescent protein (GFP)-labeled bone marrow from GFP transgenic mice, they demonstrated a high degree of chimerism in the mouse models. By two-color flow cytometry, they showed that bone marrow transplantation did not alter the percentage distribution of leukocyte subtypes. They further demonstrated that circulating immune cells derived from transplanted bone marrow retained their ability to produce TNF-α upon stimulation by phorbol esters and ionomycin, known activators of leukocytes. These are critical controls, which indicate that the lack of TNF-α production by transplanted immune cells during cisplatin nephrotoxicity is not due to their faulty behavior, further supporting the conclusion that TNF-α is produced by resident kidney cells rather than bone marrow-derived immune cells.

Although negating a role of bone marrow-derived immune cells in TNF-α production, the study by Reeves and colleagues[5] does not exclude the involvement of these cells in cisplatin nephrotoxicity. Recent work by Rabb and colleagues[6] demonstrated that, as compared with wild-type animals, T cell-deficient mice were more resistant to cisplatin nephrotoxicity. Notably, reconstitution of T cells into these animals partially restored their sensitivity to cisplatin injury.[6] Thus, immune cells, particularly the infiltrating T cells, contribute to the development of renal pathology during cisplatin treatment. Intriguingly, Rabb and colleagues also demonstrated that the production of proinflammatory cytokines, including TNF-α, was attenuated in T cell-deficient mice, suggesting a role for T cells in triggering inflammation and TNF-α production during cisplatin nephrotoxicity.[6] Apparently, there is a discrepancy between the study by Reeves and colleagues and the study by Rabb's group: the former indicates TNF-α production by resident kidney cells,[5] whereas the latter suggests the involvement of infiltrating T cells.[6] How can these findings be reconciled? One possibility is that, although TNF-α is produced mainly by resident kidney cells, infiltrating T cells may have a regulatory or stimulatory role. This scenario is supported by the observation that T-cell infiltration occurs very early (within hours) during cisplatin nephrotoxicity.[6] Is there indeed a functional interaction between infiltrating T cells and resident kidney cells that leads to TNF-α production? How do T cells regulate TNF-α production in kidney cells? Do they secrete cytokines to prime these cells? What specific cytokines do they produce? These are important questions for investigation in the future.

Despite the evidence for TNF-α production by resident kidney cells, the exact identity of the responsible cell type(s) has yet to be determined. In the kidneys, mesangial cells, glomerular cells, endothelial cells, and renal tubular cells are all capable of producing TNF-α in response to a variety of stimuli. Reeves

and colleagues showed recently that cisplatin treatment induced modest TNF-α production in cultured proximal tubular cells, which involved gene transcription and mRNA stabilization.[7] Interestingly, in combination with endotoxins, cisplatin dramatically increases TNF-α production and secretion.[8] TNF-α production following the combinatorial treatment seems to involve an intriguing regulation of protein translation via p38 mitogen-activated protein kinase and the translation initiation actor eIF4E.[8] These novel findings suggest that renal tubular cells contribute to TNF-α production during cisplatin nephrotoxicity and related pathological conditions. Certainly, this inference needs to be further established *in vivo*, ideally with the use of tubular cell-specific TNF-α knockout models. If it is proven to be true in the kidneys, then the same tubular cells are producing a noxious molecule (TNF-α) to insult themselves.

Why is it important to identify the cells that produce TNF-α during cisplatin nephrotoxicity? First, this is an essential step toward a fundamental understanding of TNF-α production and inflammation under the pathological condition. Without knowing what cells are producing TNF-α, it will be very difficult, if not impossible, to gain further insights into the underlying molecular mechanisms. Second, many cell types are capable of producing TNF-α, and the signaling pathways regulating TNF-α production in various cells can be quite different. As a result, identification of the TNF-α-producing cell type(s) may focus our effort on specific pathways in these cells for renoprotection during cisplatin treatment.

How, then, is TNF-α involved in cisplatin nephrotoxicity? As a pleiotropic cytokine, TNF-α induces a variety of cellular responses ranging from inflammation to cell death. In a given cell, there are two types of TNF-α receptors, TNFR1 and TNFR2. Binding of the receptors activates distinct, but not mutually exclusive, signaling cascades. Notably, TNFR1 contains a conserved 'death domain,' which, upon TNF-α ligation, can trigger the formation of a caspase-activation complex, leading to apoptosis. In contrast, TNFR2 does not have the 'death domain' and therefore may not be directly involved in the initiation of apoptosis. During cisplatin-induced nephrotoxicity, renal tubular cells undergo both necrotic and apoptotic cell death. Several years ago, Tsuruya and colleagues showed that proximal tubular cells isolated from TNFR1-deficient mice were more resistant to cisplatin-induced caspase activation and apoptosis, suggesting the involvement of TNF-α–TNFR1 signaling in tubular-cell apoptosis under the experimental condition.[9] On the other hand, Reeves and colleagues demonstrated the amelioration of cell death in TNFR2-deficient mice after cisplatin treatment.[10] Importantly, this and subsequent studies indicate that a major role of TNF-α is to stimulate the production of proinflammatory factors and recruit inflammatory cells. Consistent with this view, infiltration of leukocytes into the kidneys is reduced in WT→KO and KO→KO chimeric mice, suggesting that TNF-α produced by resident kidney cells is, indeed, critically important in the inflammatory response.[5] Thus TNF-α may trigger tubular-cell death and tissue damage directly via TNFR1 as well as indirectly by mounting a robust inflammatory response via TNFR2 (Figure 1). Nevertheless, while emphasizing the role of TNF-α in our discussion, it is important to recognize that cisplatin nephrotoxicity is a multifactorial process. Thus, although TNF-α is a significant contributing factor to the pathogenesis, it is unlikely to be the only one. Accordingly, pharmacological or genetic suppression of TNF-α and its signaling affords significant, but not complete, renoprotection during cisplatin nephrotoxicity.[3,5,9,10] A fascinating area for future study is to decipher how the multiple pathways or mechanisms are integrated to orchestrate a remarkable renal pathology.

Can we inhibit TNF-α to protect the kidneys from cisplatin injury? The answer is a sound yes, as demonstrated clearly by Reeves and colleagues.[3,5,10] However, it is still not clear whether inhibition of TNF-α is an effective strategy for renoprotection during cisplatin-based cancer therapy. An ideal approach for renoprotection during chemotherapy would prevent cell injury and death in the kidneys, yet preserve cell killing in tumors or cancers. Unfortunately, normal tissues (including the kidneys) and cancer cells share many of the mechanisms of cell death in response to cytotoxic insults. It is unclear whether TNF-α mediates cisplatin-induced cytotoxicity in cancers and whether inhibition of TNF-α will diminish the chemotherapeutic effects of cisplatin. Investigation in these areas may ultimately lead to the development of TNF-α-targeted strategies for renoprotection during cisplatin therapy.

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