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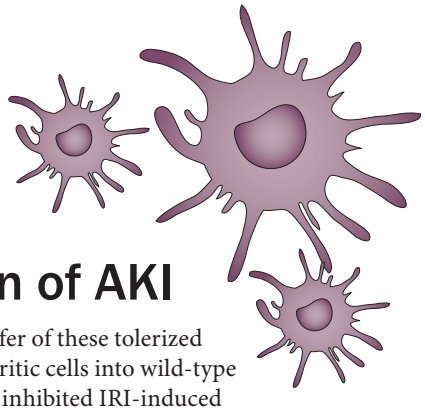

ACUTE KIDNEY INJURY

Adoptive transfer of tolerized dendritic cells—a potential new strategy for the prevention of AKI

According to new data from a study by Li Li and colleagues, adoptive transfer of dendritic cells tolerized with the selective adenosine 2A-receptor ($A_{2A}R$) agonist, ATL313, protects the kidneys of wild-type mice from ischaemia–reperfusion injury (IRI)—a model that mimics acute kidney injury (AKI) in humans. The researchers suggest that administration of dendritic cells tolerized using $A_{2A}R$ agonists could be a new therapeutic strategy for the prevention of AKI.

Previously, the researchers showed that dendritic cells and natural killer T (NKT) cells had a critical role in the initiation of the immune response to IRI in murine kidneys. In addition, activation of $A_{2A}Rs$ on immune cells using a selective agonist protected the kidneys of wild-type mice from IRI. "We hypothesised that blocking dendritic-cell-mediated NKT-cell activation could provide a new therapeutic strategy for prevention of AKI", explains principal investigator Mark Okusa.

In the present study, the researchers generated mice with selective knockout of $A_{2A}Rs$ on their dendritic cells. These $A_{2A}R$-knockout mice were more susceptible to surgery-induced kidney IRI than were wild-type mice, and the renoprotective effect of treatment with ATL313 was abrogated. The researchers concluded that activation of $A_{2A}Rs$ expressed on dendritic cells by either endogenously released adenosine or selective $A_{2A}R$ agonists protects against tissue injury.

"Because systemic administration of drugs may have untoward side effects, we wondered whether the renoprotective effect of $A_{2A}R$ agonists might be realized using an alternative approach", says Okusa. The researchers found that by treating dendritic cells *ex vivo* with ATL313 and the NKT cell glycolipid antigen αGC, they were able to produce tolerogenic dendritic cells that were specifically targeted to block dendritic-cell–NKT-cell interactions. Adoptive transfer of these tolerized dendritic cells into wild-type mice inhibited IRI-induced kidney inflammation and NKT-cell activation. Moreover, administration of the tolerized dendritic cells as early as 7 days before or as late as 6 h after surgery protected the kidneys from IRI.

"In our model, we demonstrated that $A_{2A}R$-agonist-induced dendritic cell tolerance has strong biological activity, which prevents NKT-cell-mediated innate immune activation and provide protection from kidney IRI", concludes Okusa. "Thus, we have now provided the proof-of-principle for pharmacologically tolerizing dendritic cells for use in the prevention of AKI."

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