The PO_4-tential for Less Toxic CAR T-cell Therapies

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Chimeric antigen receptor (CAR) T-cell therapy has yielded remarkable and durable responses for some patients with relapsed and refractory blood cancers. However, life-threatening toxicities such as immune effector cell–associated neurotoxicity syndrome (ICANS) remain a challenge for broad delivery of such therapies. In this issue, Tang and colleagues demonstrate an association between hypophosphatemia and CAR T cell–induced ICANS. Prospective studies are required to establish if phosphate monitoring is an early predictor for ICANS occurrence and if maintenance of phosphate levels has a role as a preventative strategy.

See related article by Tang et al., p. 1433 (4).

A recent paradigm shift has occurred in oncoimmunotherapy. Adoptive transfer of autologous chimeric antigen receptor (CAR) T cells has transformed the landscape for the treatment of relapsed and refractory blood cancers, with CD19-expressing B-cell malignancies leading the way (1). Although these therapies have produced remarkable clinical responses for patients with these malignancies, which have extremely poor prognoses, life-threatening toxicities limit the broader application of CAR T-cell therapy to settings where the risk–benefit balance is less favorable. Immune effector cell–associated neurotoxicity syndrome (ICANS; ref. 2) and cytokine release syndrome are two major toxicities that result directly from the induction of powerful immune effector responses in some patients who receive CAR T-cell therapy.

ICANS typically manifests as a toxic encephalopathy often beginning with word-finding difficulties with progressive confusion, aphasia, impaired motor function, and in its extreme forms, seizures, cerebral edema, and coma have been reported. Despite the clinical syndrome being relatively readily recognized, the pathophysiology of ICANS is incompletely understood. Factors implicated include monocyte-derived IL1, on-target off-tumor effects on $CD19^+$ brain mural cells, and cells within the infusion product that have a monocyte-like transcriptional signature, all of which have been associated with high-grade ICANS (3). Further elucidation of the pathophysiology of ICANS will permit early identification of patients at high risk for ICANS and the development of disease-modifying therapy for CAR T cell–infused patients who develop neurotoxicity.

The symptoms of acute hypophosphatemia observed with increased metabolic demand such as re-feeding syndrome and sepsis, have striking overlaps with ICANS. In this issue, Tang and colleagues explore the potential role of CAR T cell–induced hypophosphatemia in the pathogenesis of ICANS (4). To demonstrate that CAR T-cell therapy drives extracellular phosphate consumption, CD19-expressing lymphoma cells were cocultured with CD19-targeted CAR T cells that contained either CD28 or 4–1BB costimulatory domains within the CAR construct. Compared with control samples, the cocultured samples demonstrated significant depletion of extracellular phosphate. In dynamic metabolomic assays, metabolism (predominately oxidative phosphorylation) was markedly increased by CAR T cells following their engagement with their target antigen, suggesting increased phosphate consumption.

Finding that CAR T-cell cytotoxicity was associated with depletion of extracellular phosphate, Tang and colleagues retrospectively examined data from a cohort of CAR T cell–treated patients for associations with clinical hypophosphatemia. Concordant with their laboratory finds, this demonstrated that the nadir of patient serum phosphate correlated with the incidence and severity of ICANS and that there was a temporal association between the onset of ICANS and hypophosphatemia.

Together, these provocative findings add to a growing body of evidence suggesting that metabolic reprogramming is pivotal to better augmenting T-cell effector functions. Although these findings demonstrate that phosphate depletion occurs in the *in vitro* setting, it also opens questions as to whether the manipulation of extracellular phosphate is replicated *in vivo*, and if CAR T-cell function and/or safety can be enhanced through engineering toward a more favorable metabolic state. More provocative is the potential for these findings to rapidly translate to the clinical environment, either by using serum phosphate monitoring as an early predictor for ICANS occurrence and/or by therapeutic intervention to maintain phosphate levels as a preventative strategy.

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