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Immunomonitoring of patients with hepatic cancer undergoing liver transplantation after immunotherapy unravels an unexpected synergism between trained immunity and T cell memory.

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Abstract

Immunotherapy (IT) with immune-checkpoint inhibitors is becoming a universal strategy for cancer treatment. However, most solid malignancies require the combination of IT with standard therapies to achieve consistent clinical benefit. Nevertheless, the synergistic mechanisms underlying the efficacy of these different combinatorial regimens, particularly in term of immunological outcomes, are still poorly defined. IT should be combined with other oncological treatments based on a scientifically-sounded rationale to possibly potentiate, and not jeopardize, the IT-mediated priming of anti-tumor immunity. An extreme example of this concept is represented by hepatocellular carcinoma (HCC), in which IT is starting to be administered with liver transplantation (LT). Indeed, such a combination has been considered in recent clinical studies with rather promising results in terms of efficacy. Notwithstanding, the immunosuppressive regimens required for avoiding graft rejection could heavily penalize T cell responses induced by IT. Hence, how could such a combination therapy be clinically effective? This is the topic we have been recently addressing with the ImmunoXXL study (NCT05879328), a prospective clinical trial in which multimodal immunomonitoring has been applied to HCC patients undergoing IT+LT or receiving the two regimens alone. Data obtained so far suggest the occurrence of an unexpected immune synergism based on the ability of LT to sustain IT-primed T cell memory through the engagement of trained immunity, thus shedding light on the rationale of transplant oncology in solid tumors.