PNAS Plus Significance Statements

Lipid phosphatases identified by screening a mouse phosphatase shRNA library regulate T-cell differentiation and Protein kinase B AKT signaling

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We identified a series of lipid phosphatases that regulate differentiation of naïve CD4 T cells to their major phenotypic states, T-helper (Th)1/Th2/Th17. Previously, phosphatase and tensin homolog (PTEN) was the only lipid phosphatase shown to function in this process. To identify these phosphatases, we used a unique "phosphatase-wide" screening procedure. Our results (pp. E1849–E1856) demonstrate that myotubularin-related protein (MTMR) 9 and MTMR7 play critical roles in Th differentiation. Knocking down MTMR9 enhances Th1 priming, and such Th1 cells show increased protein kinase B (PKB)/AKT phosphorylation. Knocking down MTMR7 increases Th2 and Th17 priming; these cells show enhanced AKT phosphorylation.

Central role of liver in anticancer and radioprotective activities of Toll-like receptor 5 agonist

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Toll-like receptor 5 (TLR5) is an innate immunity receptor that specifically recognizes and triggers immune response to bacterial flagellins. In addition to resistance to *Salmonella* infection, TLR5 agonists protect mammals from radiation and have anticancer effects, including suppression of tumor metastases. Using mouse models (pp. E1857–E1866), we defined the liver as a major target for TLR5 agonists. Administration of pharmacologically optimized flagellin derivative CBLB502 leads to rapid activation of prosurvival nuclear factor kappa B (NF-κB) and STAT3 pathways in the liver and rescues mice from lethal doses of hepatotoxic Fas-agonistic antibodies. Thus, TLR5 agonists can be considered for treatment and prevention of liver metastasis and hepatoprotective applications.

Engineering recombinant reoviruses with tandem repeats and a tetravirus 2A-like element for exogenous polypeptide expression

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Recombinant reoviruses that can propagate autonomously while expressing exogenous polypeptides over multiple growth cycles have proven difficult to generate but seem plausible to try to develop as potential vaccine vectors. Here (pp. E1867–E1876) we report a strategy for engineering such reoviruses that express portions of the simian immunodeficiency virus Gag protein. The strategy has been applied so far to 3 of the 10 reovirus genome segments and can also be used to map the terminal regions required for segment packaging. Gag-specific T-cell responses induced in mice by one of these recombinant reoviruses support their potential utility as vectors for immunogen expression.