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In This Issue

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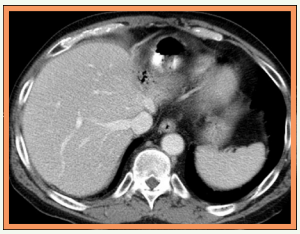
In this issue

TRPM4 keeps blood pressure down Hypertension is a risk factor for many serious health conditions, including stroke, end-stage renal disease, and heart disease. However, in most patients, the underlying cause is unknown. Increased understanding of the regulation of blood pressure might provide new insight into the pathogenesis of hypertension. In this context, Mathar and colleagues have identified a role for transient receptor potential cation channel, subfamily M, member 4 (TRPM4) in regulating blood pressure in mice (3267–3279). Initial analysis indicated that TRPM4 was expressed in cells and tissues of the mouse cardiovascular system, suggesting a role for TRPM4 in this system. Consistent with this, Trpm4–/– mice were hypertensive and developed cardiac hypertrophy at 6–8 months of age. Further analysis revealed the mechanism underlying the increased blood pressure in Trpm4–/– mice. Specifically, lack of TRPM4 in chromaffin cells in the adrenal gland caused increased release of catecholamines, leading to increased sympathetic tone and hypertension. The authors therefore conclude that TRPM4 limits catecholamine release from chromaffin cells and that disruption of this control, as occurs in mice lacking TRPM4, increases blood pressure. They further suggest that boosting TRPM4 activity might help limit blood pressure increases in patients with hypertension. Improving RNAi efficacy, toxicity, and persistence RNAi-based therapies have been well tolerated in clinical trials. However, animal studies suggest that there is a […]

Boosting the efficacy of anticancer vaccines



There are several challenges to be overcome if therapeutic anticancer vaccines, which are designed to boost the patient's anticancer immune response, are to be successfully developed. For example, more effective ways to deliver antigen to in situ DCs, which then activate tumor-specific T cell and antibody responses, are needed. The viral vectors used thus far to deliver antigen have elicited vector-specific neutralizing antibodies and Tregs, precluding their effective clinical use. But now, Morse and colleagues, have developed a way to overcome the neutralizing antibodies and increased numbers of Tregs by using an alphavirus packaged in virus-like replicon particles (VRP) (3234–3241). Repeated administration of VRP containing alphavirus carrying the gene encoding the tumor antigen carcinoembryonic antigen (CEA) to patients with metastatic cancer expressing CEA induced clinically relevant immune responses. For example, the CEA-specific antibodies that were generated killed tumor cells from human colorectal cancer metastases. Importantly, the presence of CEA-specific T cell responses was associated with longer overall patient survival. The authors therefore suggest that VRP-based vectors could be used to overcome immune-suppressive mechanisms in many cancer settings.

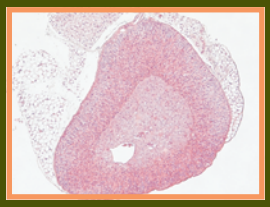
Improving RNAi efficacy, toxicity, and persistence

RNAi-based therapies have been well tolerated in clinical trials. However, animal studies suggest that there is a need for caution in their further clinical development, as RNAi can trigger cytotoxicity leading to organ failure and lethality. It is believed that these adverse effects are a result of saturation of endogenous cellular microRNA machinery such as exportin-5 (Xpo-5). Grimm and colleagues have now generated substantive data in mice to support the idea that high doses of RNAi-based therapies overload the endogenous microRNA pathway, resulting in hepatotoxicity (3106–3119). They identify some of the most vulnerable cellular steps while providing insights into how to resolve this problem. Members of the human Argonaute (Ago) family of proteins were found to be involved in saturation of endogenous cellular RNAi, with Ago-2 particularly prone to saturation and acting as a rate-limiting determinant of in vitro and in vivo RNAi efficacy and toxicity. This issue was overcome in mice using vector-based Ago-2/Xpo-5 coexpression, which enhanced RNAi silencing in the liver, reduced hepatotoxicity, and extended RNAi stability. Minimizing shRNA expression also reduced hepatotoxicity while permitting long-term gene silencing. While these data identify limitations to the use of RNAi-based therapies, they also provide optimism for their future clinical development.

ROCK2 'n' roll target for treating autoimmunity

Inappropriate and excessive production of the cytokines IL-17 and IL-21 has been linked to the pathogenesis of several autoimmune disorders, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Understanding the molecular mechanisms underlying this aberrant cytokine production might allow researchers to identify new therapeutic targets. In this issue, Biswas and colleagues have generated data in mice that indicate that Rho-associated, coiled-coil–containing protein kinase 2 (ROCK2) might be a good therapeutic target in this context (3280–3295). Initial analysis indicated that ROCK2 was activated in mouse $CD4^+$ T cells that produce high levels of IL-17 — both normal mouse $CD4^+$ T cells cultured under conditions that skew toward IL-17 production and IL-17–producing $CD4^+$ T cells from two different mouse models of spontaneous autoimmunity — and that it phosphorylated interferon regulatory factor 4 (IRF4), a transcription factor that is absolutely required for the production of IL-17 and IL-21. Importantly, administration of a ROCK inhibitor to mice with spontaneous disease modeling either RA or SLE decreased production of IL-17 and IL-21 and ameliorated disease symptoms, providing a rationale for the authors' suggestion that ROCK2 could be a good therapeutic target for the treatment of autoimmune disorders.

TRPM4 keeps blood pressure down



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