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In This Issue

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Melanocyte-like cells trigger afib The source and mechanisms underlying the ectopic beats that initiate atrial fibrillation (AF) are unclear. Levin and colleagues have now identified a population of melanocyte-like cells in the atrium and pulmonary veins of mice and humans and uncovered evidence in mice that indicates that these cells contribute to atrial arrhythmias (3420–3436). They identified a population of cells in the atrium and pulmonary veins of mice and humans that expressed dopachrome tautomerase (DCT), an enzyme involved in melanin synthesis. Single-cell transcriptional profiling showed that Dct-expressing cells in the mouse heart were distinct from both atrial myocytes and dermal melanocytes, although in vitro analysis indicated that they were excitable and exhibited action potentials similar to atrial myocytes. Adult mice lacking Dct were susceptible to induced and spontaneous atrial arrhythmias, and their cardiac melanocyte-like cells exhibited abnormal action potentials in vitro. As mice lacking both melanocyte-like cells in the heart and Dct failed to develop either induced or spontaneous atrial arrhythmias, the authors suggest that dysfunctional melanocyte-like cells in the heart may be a trigger of AF. Tregs predict outcome of West Nile virus infection Infection with West Nile virus (WNV) causes no symptoms in most people, but can cause fever, meningitis, and/or encephalitis in others. Lanteri and colleagues set out to investigate whether the number and/or function […]

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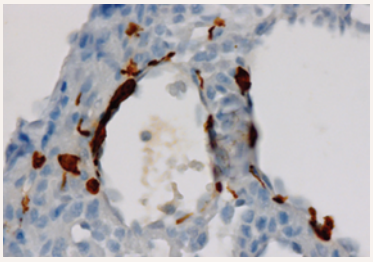
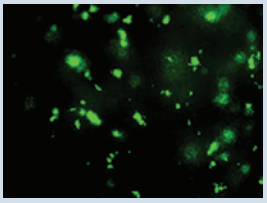


The source and mechanisms underlying the ectopic beats that initiate atrial fibrillation (AF) are unclear. Levin and colleagues have now identified a population of melanocyte-like cells in the atrium and pulmonary veins of mice and humans and uncovered evidence in mice that indicates that these cells contribute to atrial arrhythmias (3420–3436). They identified a population of cells in the atrium and pulmonary veins of mice and humans that expressed dopachrome tautomerase (DCT), an enzyme involved in melanin synthesis. Single-cell transcriptional profiling showed that Dct-expressing cells in the mouse heart were distinct from both atrial myocytes and dermal melanocytes, although in vitro analysis indicated that they were excitable and exhibited action potentials similar to atrial myocytes. Adult mice lacking Dct were susceptible to induced and spontaneous atrial arrhythmias, and their cardiac melanocyte-like cells exhibited abnormal action potentials in vitro. As mice lacking both melanocyte-like cells in the heart and Dct failed to develop either induced or spontaneous atrial arrhythmias, the authors suggest that dysfunctional melanocyte-like cells in the heart may be a trigger of AF.

FGFR4: an oncogene in rhabdomyosarcoma?

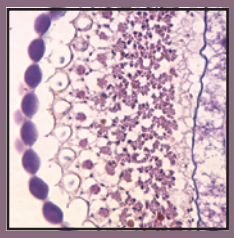


Rhabdomyosarcoma (RMS) is the most commonly diagnosed pediatric soft tissue sarcoma, and little is known about the factors that control tumor progression and metastasis. Taylor and colleagues now find that the receptor tyrosine kinase FGFR4 has a role in RMS progression (3395–3407). Initial analysis indicated that higher levels of *FGFR4* mRNA in human RMS tumor samples were associated with advanced-stage cancer and poor survival. Conversely, knocking down *FGFR4* expression in a human RMS cell line decreased its ability to grow and metastasize when xenotransplanted into immunocompromised mice. Further analysis identified mutations in the tyrosine kinase domain–encoding region of *FGFR4* in 7.5% of primary human RMS tumor samples analyzed. Two of the FGFR4 mutants generated by these mutations were analyzed and found to cause constitutive activation and to lead to increased proliferation, invasiveness, and metastasis in a murine RMS cell line. Treatment with a pharmacologic inhibitor of FGFRs made the murine RMS cells expressing the FGFR4 mutants sensitive to apoptosis, leading to the conclusion that *FGFR4* acts as an oncogene in RMS and that targeting FGFR4 might be of therapeutic benefit in RMS.

Tregs predict outcome of West Nile virus infection

Infection with West Nile virus (WNV) causes no symptoms in most people, but can cause fever, meningitis, and/or encephalitis in others. Lanteri and colleagues set out to investigate whether the number and/or function of Tregs, a $CD4^+$ T cell population that suppresses effector T cell responses, differed in individuals with asymptomatic and symptomatic WNV infection (3266–3277). Analysis of blood donated by 32 individuals acutely infected with WNV indicated that the frequency of Tregs (defined as $CD4^+CD25^+CD127^{low}CD152^+$) increased substantially following infection. However, individuals who were asymptomatic had higher levels of Tregs than those who exhibited symptoms of infection. Similar observations were made in mice infected with WNV. Consistent with a role for Tregs in controlling the symptoms of WNV infection, mice lacking Tregs (defined as $CD4^+CD25^+CD152^+Foxp3^+$) were more susceptible to lethal infection with WNV than control mice. Therefore, higher levels of peripheral Tregs after infection with WNV may protect against severe disease in immunocompetent individuals.

α-Synuclein phosphorylation: a balancing act in Parkinson disease



Both genetic and pathologic data indicate a role for the neuronal protein α-synuclein in the pathogenesis of Parkinson disease. Previous studies have indicated that phosphorylation of α-synuclein Ser129 is a key event in α-synuclein–mediated neurotoxicity. Chen and colleagues have identified a counterbalancing role in neuroprotection for phosphorylation of α-synuclein Tyr125 (3257–3265). Specifically, in *Drosophila* transgenic for human α-synuclein, phosphorylation of human α-synuclein Tyr125 was detected and shown to protect from α-synuclein neurotoxicity. The two phosphorylated amino acids were shown to have opposing roles when the authors observed that Tyr125 phosphorylation decreased levels of toxic soluble α-synuclein oligomers in the *Drosophila* brain, whereas Ser129 phosphorylation increased them. Tyr125 phosphorylation was found to decrease as both humans and *Drosophila* aged and was reduced in cortical tissue from patients with synucleinopathy dementia with Lewy bodies, a disease related to Parkinson disease. Therefore, changes in the balance between Ser129 and Tyr125 phosphorylation — which promote neurotoxicity and neuroprotection, respectively — might cause α-synuclein neurotoxicity in Parkinson disease and related disorders.