Alcohol, Edema, and Traumatic Brain Injury

While the role of ethanol consumption prior to traumatic brain injury (TBI) in aggravating morbidity and mortality remains controversial, the negative effects of brain edema are well established. Katada et al (Am J Pathol 2012, 180:17–23) hypothesized that TBI-related brain edema is significantly potentiated by ethanol-induced expression of the water channel aquaporin-4 (AQP4). In rats acute ethanol administration increased AQP4 expression after TBI, leading to severe brain edema. Ethanol pretreatment induced lipid peroxidation as well as expression of NF-κB and hypoxia-inducible factor-1α after TBI. An AQ4 inhibitor (acetazolamide) improved the survival rate to 100% and decreased brain edema and AQP4 expression. These data suggest that AQP4 inhibition may reduce morbidity and mortality in alcohol-intoxicated TBI patients as well as in those with ischemic brain injury or brain tumor edema.

Renal DCs in Tubulointerstitial Damage and Fibrosis

Renal dendritic cells (DCs), which may participate in local inflammation, exist in heterogeneous populations that share surface marker overlap with monocytes/macrophages. Using unilateral ureteral obstruction (UUO) as a model inflammatory disease, Snelgrove et al (Am J Pathol 2012, 180:91–103) sought to define the role of DCs in the kidney. Renal DCs underwent morphological and functional changes (increased CD11b and less F4/80 expression) in the injured kidney, consistent with a pro-inflammatory phenotype. The low capacity of renal DCs to induce T-cell proliferation was increased in the UUO inflammatory milieu. Depletion studies showed that although renal CD11c+ cells became activated, renal DCs did not directly contribute to apoptosis or fibrosis in the early stages after UUO. In the context of interstitial inflammation, renal DCs function more effectively as antigen-presenting cells than as contributors to tubulointerstitial damage and fibrosis.

Th17 Cells Express Histamine H4 Receptor

The histamine H4 receptor (H4R) is functionally expressed on Th2-polarized CD4+ T cells. IL-17–producing T cells (Th17 cells), another CD4+ T-cell subset, are found in psoriatic plaques and in acute skin lesions of atopic dermatitis where histamine is also present in high concentrations. Mommert et al (Am J Pathol 2012, 180:177–185) examined the role H4R on Th17 cells. In vitro activated Th17 cells expressed H4R mRNA and protein. IL-17–positive cells from psoriatic skin lesions were also positive for functional H4R, and stimulation with histamine or an H4R agonist increased IL-17 production and induced activating protein-1 in Th17 cells. Thus, histamine might foster the immunomodulatory potency of skin-infiltrating Th17 cells in inflammatory skin diseases such as psoriasis and atopic dermatitis.

Understanding the Molecular Mechanisms of Dementia

In several neurodegenerative disorders, pathological TDP-43 mislocalizes from its nuclear location to the cytoplasm, where it is proteolytically cleaved to form C-terminal fragments. Caccamo et al (Am J Pathol 2012, 180:293–302) examined the 25-kDa C-terminal fragment of TDP-43 (TDP-25) to discern its role in disease pathogenesis. Transgenic mice expressing TDP-25 developed cognitive deficits associated with the build-up of soluble TDP-25. These cognitive deficits were independent of TDP-43–positive inclusions, occurring without overt neurodegeneration. Additionally, TDP-25 expression was sufficient to alter the processing of endogenous full-length TDP-43. These data provide a framework for understanding the molecular mechanisms underlying the onset of cognitive deficits in TDP-43 proteinopathies, such as frontotemporal lobar degeneration cases (FTLD-TDP), motor neuron disease, and amyotrophic lateral sclerosis.

Drug-Resistant Dormancy in Cancer

Tumor recurrence from remnant tumor cells presents an important challenge to the success of cancer chemotherapy, with drug-resistant cells persisting and sustaining the tumor or entering dormancy before igniting a future relapse. Kinoshita et al (Am J Pathol 2012, 180:375–389) examined the mechanisms of such relapse in cultured high-grade ovarian carcinoma cells. Partial knockdown of nucleoporin p62 (NUP62; of the nuclear pore complex) by small-interfering RNA conferred cisplatin resistance. Treatment with NUP62 small-interfering RNA and cisplatin left resistant cells in a state of dormancy; some dormant cells could be induced to proliferate by transient induction of NUP62 expression from an ectopic expression construct. The modulation of nuclear pore architecture represents a novel mechanism through which tumor cells could acquire transient resistance to certain chemotherapeutic agents, and the culture system provides a novel experimental window into the dynamics of tumor cell drug resistance and dormancy.