Sulić S, Panić L, Barkić M, Mercep M, Uzelac M, Volarević S. Inactivation of S6 ribosomal protein gene in T lymphocytes activates a p53-dependent checkpoint response. Genes Dev. 2005;19:3070-82.

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Ribosome biogenesis has been associated with regulation of cell growth and cell division, but the molecular mechanisms that integrate the effect of ribosome biogenesis on these processes in mammalian cells remain unknown. To study the effect of impaired ribosome functions in vivo, the authors conditionally deleted one or two alleles of the 40S ribosomal protein S6 gene in T cells in the mouse. While complete deletion of S6 abrogated T-cell development, hemizygous expression did not have any effect on T-cell maturation in the thymus, but inhibited the accumulation of T cells in the spleen and lymph nodes, as a result of their decreased survival in the peripheral lymphoid organs. Additionally, TCR-mediated stimulation of S6-heterozygous T cells induced a normal increase in their size, but cell cycle progression was impaired. Genetic inactivation of p53 tumor suppressor rescued development of S6-homozygous null thymocytes and proliferative defect of S6-heterozygous T cells. These results demonstrate the existence of a p53-dependent checkpoint mechanism that senses changes in the fidelity of the translational machinery to prevent aberrant cell division or eliminate defective T cells in vivo. Failure to activate this checkpoint response could potentially lead to a development of pathological processes such as tumors and autoimmune diseases.

Sapunar D, Modrić-Jednačak K, Grković I, Michalkiewicz M, H Hogan Q. Effect of peripheral axotomy on pain-related behavior and dorsal root ganglion neurons excitability in NPY transgenic rats. Brain Res. 2005;1063:48-58.

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In order to clarify the physiologic role of NPY in sensory processing, the authors obtained intracellular recordings of DRG neurons from wild type (WT) and NPY overexpressing transgenic rats (NPY-TG) before and after injury. The authors investigated medium and large diameter DRG neurons since up-regulation of NPY peptide following the nerve injury occurs primarily in those cells. Neurons were classified as $A_{alpha/beta}$ and A_{delta} using conduction velocity and action potential duration. Prior to the injury, $A_{alpha/beta}$ neurons of NPY-TG rats conducted more slowly and had a more brief AHP than similar cells from the WT group. Adelta neurons at baseline conducted faster in TG animals compared to WT. Ligation of the 5th lumbar spinal nerve (SNL) produced certain changes in $A_{alpha/beta}$ cells that were evident only in the TG group. These include increased refractory period, increased input resistance, AHP prolongation and a depolarizing shift in threshold for AP initiation. The expected injury-induced CV slowing was not seen in NPY-TG $A_{alpha/beta}$ cells. In the A_{delta} cell group, injury produced a depolarizing shift in the resting membrane potential, an increase in AP duration and decrease in AHP and refractory period duration only in WT rats, while NPY-TG cells lacked these injury-induced changes. Behavior tests showed diminished sensory response to nerve injury in NPY-TG rats, ie, shorter duration of enhanced pain-related behavior and attenuation of contralateral effect. In conclusion, these observations suggest that NPY overexpression leads to reduced neuronal activity following nerve injury in a cell-specific manner.

Baus-Lončar M, Kayademir T, Takaishi S, Wang T. Trefoil factor family 2 deficiency and immune response. Cell Mol Life Sci. 2005;62:2947-55.

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The protective effect of Trefoil Factor Family (TFF) proteins in the gastrointestinal tract by promoting the healing of injured mucosa is well known. An increasing body of evidence connects TFFs, especially, TFF2 and TFF3, with a possible role in immune regulation. TFF2 is able to inhibit lipopolysaccharide-induced nitric oxide production in

monocytes and can potently limit leukocyte recruitment at the site of injury. An analysis of gene expression in gastrointestinal tissue of TFF2-deficient mice reveals some new aspects of TFF2's role in the immune response.

Judaš M, Radoš M, Jovanov-Milošević N, Hrabac P, Štern-Padovan R, Kostović I. Structural, immunocytochemical, and MR imaging properties of periventricular crossroads of growing cortical pathways in preterm infants. AJNR Am J Neuroradiol. 2005;26:2671-84.

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Periventricular white matter (WM) areas are widely recognized as predilection sites for complex cellular damage after ischemia/reperfusion or inflammatory injury of the perinatal cerebrum. The authors analyzed histochemical and MR imaging properties of fiber architectonics and extracellular matrix (ECM) of periventricular areas to disclose the potential significance of topographically specific WM lesions for the neurodevelopmental outcome. The authors combined histochemical methods for demonstration of fibers, axonal guidance molecules, and ECM with T1-weighted MR images on postmortem specimens aged 15 to 36 postovulatory weeks (POW) and T2-weighted MR images on in vivo fetuses aged 14 to 26 POW. The fiber architectonics of the fetal cerebrum display tangential axon strata in frontopolar and occipitopolar regions, whereas the central periventricular region contains crossroads of intersecting callosal (transverse), associative (sagittal), and thalamocortical/corticofugal (radial) fiber bundles. In early preterms, crossroads contain hydrophylic ECM with axonal guidance molecules, and they are easily recognized as hypointensities on T1-weighted MR images or hyperintensities on T2-weighted MR images. After the 28 POW, tangential fetal fiber-architectonic stratification transforms into the corona radiata system; however, the growth of cortical pathways continues in crossroad areas, as indicated by the presence of ECM and their distinct MR imaging signal intensities. The correlation of MR imaging with histochemical findings demonstrated the presence of periventricular fiber crossroads rich in ECM and axonal guidance molecules. The authors propose that, in perinatal WM lesions, periventricular WM crossroads represent a hitherto unrecognized and vulnerable cellular and topographic target in which combined damage of association-commissural and projection fibers may explain the complexity of cognitive, sensory, and motor deficit in survivors of periventricular WM lesions.

Morović M. Q Fever pneumonia: are clarithromycin and moxifloxacin alternative treatments only? Am J Trop Med Hyg. 2005;73:947-8.

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Medical records of 77 patients with Q fever pneumonia that was serologically confirmed by enzyme-linked immunosorbent assay were studied to compare the clinical efficacy of doxycycline, clarithromycin, and moxifloxacin. The mean times to defervescence were 2.4 days for those receiving doxycycline, 1.9 days for those receiving clarithromycin, and 2.2 days for those receiving moxifloxacin. There were no interruptions of the regimens in any groups because of side effects, and outcome was favorable in all patients with no complications or relapses during follow-up. This efficacy of clarithromycin and moxifloxacin, together with their safety profiles, suggest that these alternative agents in the treatment of Q fever pneumonia could also be used as the first-line therapy.

Šantić M, Molmeret M, Klose KE, Abu Kwaik Y. Francisella tularensis travels a novel, twisted road within macrophages. Trends Microbiol. 2006;14:37-44.

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Francisella tularensis is a highly infectious intracellular bacterium that causes fulminating disease and is a potential bioweapon. Although entry of the bacteria into macrophages is mediated by novel asymmetric, spacious pseudopod loops, the nascent phagosome becomes tight fitting within seconds of formation. Biogenesis of the Francisella-containing phagosome (FCP) is arrested for 2-4h at a unique stage within the endosomal-lysosomal degradation pathway, followed by gradual bacterial escape into the cytosol, where the microbe proliferates. By contrast, other intracellular pathogens either proliferate within an idiosyncratic phagosome or escape within minutes into the cytoplasm to avoid degradation. Thus, trafficking of the FCP defies the dogma of classification of intracellular pathogens into vacuolar or cytosolic. The Francisella pathogenicity island and its transcriptional regulator MglA are essential for arresting biogenesis of the FCP. Despite sophisticated microbial strategies to arrest phagosome biogenesis within quiescent macrophages, trafficking of F. tularensis and other intracellular pathogens within interferon-gamma-activated macrophages is similar, in that the bacterial phagosomes fuse to lysosomes. The potential use of F. tularensis as a bioweapon has generated interest in the study of its molecular pathogenesis to identify targets for therapy, vaccination and rapid diagnosis.

Faubel S, Ljubanović D*, Poole B, Dursun B, He Z, Cushing S, et al. Peripheral CD4 T-cell depletion is

not sufficient to prevent ischemic acute renal failure. Transplantation. 2005;80:643-9.

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Ischemia reperfusion injury leading to acute renal failure (ARF) and delayed graft function is an important problem in organ transplantation. CD4+ T cells, essential for transplant rejection, may mediate ischemic ARF. The authors have demonstrated that the caspase-1 mediated production of IL-18 is pathogenic in ischemic ARF in mice. A potential source of IL-18 in ischemic ARF is the CD4+ T cell. The authors therefore examined the effect CD4+ T cell depletion on the development of ischemic ARF and the activation of IL-18. Functional and histological correlates were examined in two groups of mice with ischemic ARF: 1) CD4 T-cell depleted with the antibody GK1.5, and 2) T-cell receptor alpha-chain deficient (TCRalpha $^{-/-}$) mice. TCRalpha $^{-/-}$ mice lack the alpha chain of the T-cell receptor and therefore lack functional CD4+ and CD8+ T cells. Flow cytometry of lymph nodes and immunohistochemistry of kidneys demonstrated complete depletion of CD4+ T cells in mice with ischemic ARF treated with GK 1.5. CD4+ T-cell depletion did not confer functional (serum creatinine, BUN and FITC-labeled inulin clearance) or histological protection against ischemic ARF. Likewise, TCRalpha $^{-/-}$ mice were not protected against ischemic ARF. Renal caspase-1 activity and IL-18 protein were similar in CD4+ T-cell depleted and wild-type postischemic reperfusion. In conclusion, ischemic ARF can occur in the absence of classical T-cell function. The evaluation of other inflammatory mediators (eg, macrophages or NK cells) as a source of IL-18 and mediator of ischemic ARF warrants further investigation.

Grubić Z, Štingl K, Čečuk Jeličić E, Žunec R, Kaštelan A, Serventi Seiwerth R, et al. Repetitive DNA polymorphisms in following chimerism after allogeneic bone marrow transplantation. Clin Transplant. 2005;19:586-90.

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Information about the chimeric status of patients is of great importance in comparison of different conditioning and prophylactic regimens as well as for the post-bone marrow transplantation (BMT) therapies. In some cases, mixed chimerism (MC) can also be predictive of relapse. Analysis of the short tandem repeats (STR) loci by polymerase chain reaction (PCR) is a choice method for this purpose. In this study, we monitored 15 patients after BMT. Twelve of them underwent classical-conditioning regimen while the remaining three patients were subjected to non-myeloablative conditioning (minitransplantation). Evaluation of chimerism was performed using five STR and one variable number of tandem repeats (VNTR) locus. Four additional loci were PCR-amplified in cases of minitransplantation. Samples were analyzed by electrophoresis in an ALFexpress sequencer. MC was detected in seven cases of which it was predictive of relapse for two patients, who suffered from acute lymphocytic leukemia (ALL). The PCR-STR method proved to be a fast and relatively simple method, while the tested STR loci showed a high level of informativeness.

Brčić-Kostić K. Neutral mutation as the source of genetic variation in life history traits. Genet Res. 2005;86:53-63.

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The mechanism underlying the maintenance of adaptive genetic variation is a long-standing question in evolutionary genetics. There are two concepts (mutation-selection balance and balancing selection) which are based on the phenotypic differences between alleles. Mutation - selection balance and balancing selection cannot properly explain the process of gene substitution, ie, the molecular evolution of quantitative trait loci affecting fitness. I assume that such loci have non-essential functions (small effects on fitness), and that they have the potential to evolve into new functions and acquire new adaptations. Here the author shows that a high amount of neutral polymorphism at these loci can exist in real populations. Consistent with this, rhe author proposes a hypothesis for the maintenance of genetic variation in life history traits which can be efficient for the fixation of alleles with very small selective advantage. The hypothesis is based on neutral polymorphism at quantitative trait loci and both neutral and adaptive gene substitutions. The model of neutral – adaptive conversion (NAC) assumes that neutral alleles are not neutral indefinitely, and that in specific and very rare situations phenotypic (relative fitness) differences between them can appear. In this paper the author focuses on NAC due to phenotypic plasticity of neutral alleles. The important evolutionary consequence of NAC could be the increased adaptive potential of a population. Loci responsible for adaptation should be fast evolving genes with minimally discernible phenotypic effects, and the recent discovery of genes with such characteristics implicates them as suitable candidates for loci involved in adaptation.