JCI The Journal of Clinical Investigation

In This Issue

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J Clin Invest. 2001;108(10):1409-1409. https://doi.org/10.1172/JCI119938.

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Cholesterol-independent benefits of statins in cardiac hypertrophy (See article on pages 1429–1437.) The statin drugs are best known for their ability to block cholesterol biosynthesis and have been widely prescribed to people at risk of heart disease because of high serum cholesterol. Takemoto and coworkers have now identified another beneficial effect of these drugs that might make them suitable for treating a different set of heart patients, those with cardiac hypertrophy. The hypertrophic response in cardiac myocytes entails not just an increase in cell size, but also a reversion to a pattern of gene expression normally seen only in early heart development. Statins, which block mevalonate biosynthesis, prevent cells from producing a variety of this lipid's metabolites, including some that become covalently linked to important regulatory proteins. Small, GTP-binding proteins of the Rho family, particularly Rac1, are lipid-modified and play a crucial role in remodeling the actin cytoskeleton when cells move or change shape. Takemoto et al. confirm here that lipid-linked Rac1 is also key to the hypertrophic response, and they show that reactive oxygen species, formed specifically in cells with an active and properly localized Rac1 protein, drive myocyte hypertrophy, both in living animals and in cells. The antioxidant effect of the statins, mediated by Rac, is independent of its effects as a cholesterol lowering agent, since the anti-hypertrophic […]

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Dendritic cell–based vaccination to prevent opportunistic fungal infections

(See article on pages 1469–1474.)

Because HIV depletes the population of $CD4^+$ T cells, AIDS patients and others with immunosuppressive conditions are in a poor position to mount a protective response to vaccines. The absence of T cell help is particularly troublesome because of the opportunistic infections that are common among these patients. Noting that $CD4^+$ cell-independent immunization would be useful to protect immunosuppressed people from infection by the fungus *Pneumocystis carinii*, Zheng et al. have tested a strategy that was recently developed to induce mucosal antibodies against a bacterial pathogen. This approach relies on dendritic cells (DC), which normally express the receptor CD40 and can be activated by the T cell–borne CD40 ligand, CD40L. Transfecting DC with the CD40L circumvents this step, allowing the DC to activate antigen-specific B cells directly. Zheng et al. generated mouse DC, transfected them with CD40L, and "pulsed" them in vitro with *Pneumocystis carinii*, allowing them to display the pathogen's peptides on their surface. As anticipated, the resulting DC conferred significant and apparently lasting protection against *Pneumocystis* pneumonia on mice, even though the host animals lacked endogenous CD4+ T cells. If DC from HIV infected individuals are capable of activating human B cells in this way, such an approach could provide an important adjunct to the standard antiretroviral therapies.

Arsenic and old telomeres

(See article on pages 1541–1547.)

Telomeres, the simple repeat structures that cap each end of chromosomes, are required for chromosomal stability both in the short and long run. Over the course of one or more generations, a gradual loss of sequence from the chromosomes, occurring at each cell division, would eventually erase crucial genetic information from the genome if the cell had no mechanism to rebuild the telomere. In addition, because short or missing telomeres predispose chromosomes to fuse and create abnormal structures that cannot be assorted properly during mitosis, their disappearance could lead otherwise normal cells to undergo apoptosis — or, in some cases, to become transformed and generate tumors. Telomerase, the enzyme responsible for adding telomere repeats to the end of each chromosome, prevents both gradual chromosomal degradation and sudden loss of normal cell function. However, because telomerase activation is one means by which cancer cells escape normal growth control, this enzyme must be tightly regulated, and there has been considerable interest in blocking its function or expression. Now Chou et al. report that one of the oldest known agents in medical history has just such an effect. They show here that the toxic metal arsenic, which has proved helpful in controlling otherwise intractable leukemias, blocks transcription of one of the telomerase subunits in an apparently specific fashion. Treating tumor cells with moderate levels of arsenic mimics the effect seen in cells lacking telomerase, including shortening of the telomeres and the accumulation of structurally abnormal chromosomes. The transcriptional silencing of the telomerase subunit by arsenic is not fully understood, but it appears to involve the oxidative inhibition of the transcription factor Sp1.