

Intramural papers of the month

By Aleksandra Adomas, Heather Franco, and Mallikarjuna Metukuri

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Ribonucleotides direct the mismatch repair machinery to DNA sequence errors

NIEHS scientists in the DNA Replication Fidelity Group demonstrated that ribonucleotides in the nuclear genome mark new DNA strands for error correction by the mismatch repair (MMR) machinery. Since MMR defects cause genome instability and are associated with human diseases such as cancer, understanding the mechanism of MMR may eventually provide insight into the etiology of multiple human diseases.

The researchers found that the leading strand DNA polymerase has a sequence, conserved in all eukaryotes, associated with increased ribonucleotide incorporation. Because these ribonucleotides can cause genome instability, this conservation is justified only if ribonucleotide incorporation serves a positive function as well. The researchers hypothesized that strand signaling for MMR could be one such positive function.

Using the yeast *Saccharomyces cerevisiae*, the researchers demonstrated that ribonucleotide excision repair was necessary for optimal MMR, and that variants of the leading strand DNA polymerase, which incorporate more or less ribonucleotides than the wild type, have correspondingly more or less efficient MMR. Together, the data suggest that ribonucleotides contribute to marking the newly copied DNA strand for MMR. **(HF)**

Citation: [Lujan SA, Williams JS, Clausen AR, Clark AB, Kunkel TA.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23603118>)

2013. Ribonucleotides are signals for mismatch repair of leading-strand replication errors. *Mol Cell* 50(3):437-443.

Beta-arrestin-2 is major player in development of abdominal aortic aneurysm

NIEHS researchers determined that the signaling protein beta-arrestin-2 contributes to formation of abdominal aortic aneurysm (AAA) in mice. In humans, AAA is a largely asymptomatic, but potentially life-threatening disease that affects the aorta, the largest artery in the body. Currently, there are no pharmacological treatments available for AAA, but the present study offers a possible therapeutic breakthrough, by suggesting that beta-arrestin-2 may be a target for designing new drugs.

The authors used a mouse model of AAA, which involves the infusion of angiotensin II hormone in mice deficient for beta-arrestin-2. They observed a reduction in the incidence and severity of aneurysm formation. The underlying mechanism for beta-arrestin-2-mediated AAA formation was the activation of extracellular signal-regulated kinases that regulate expression of proinflammatory enzyme, cyclooxygenase-2 (COX-2). The beta-arrestin-2 deficiency diminished expression of COX-2 and other inflammatory factors, and it reduced macrophage infiltration in the aortas.

Angiotensin II leads to AAA development, by activating a G-protein coupled receptor AT1a, which can also form a complex with beta-arrestin-2. The new findings suggest that beta-arrestin-2 contributes to aneurysm formation through a G-protein-independent AT1a signaling pathway. Since both pathways are pharmacologically different, it offers a promise of potential new treatments. **(AA)**

Citation: [Trivedi DB, Loftin CD, Clark J, Myers P, DeGraff LM, Cheng J, Zeldin DC, Langenbach R.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23524589>)

2013. Beta-arrestin-2 deficiency attenuates abdominal aortic aneurysm formation in mice. *Circ Res* 112(9):1219-1229.

The role of p53 during bacterial pneumonia

NIEHS researchers recently discovered that the transcription factor p53 modulates host defense through regulating microbicidal function and fate of phagocytes during bacterial pneumonia. This study revealed a fundamental link between defense of genome and of host during environmental insult.

The authors used mice that had their p53 genes deleted (p53^{-/-}) or in which p53 was pharmacologically inhibited. Both sets of

mice displayed enhanced clearance of extracellular bacteria during pneumonia. The lungs of p53^{-/-} mice displayed genome-wide induction of NF-kappaB response element-enriched proinflammatory genes in the steady state, and enhanced induction of cytokines upon infection. In addition, upon infection, p53-deficient mice exhibited increased influx of neutrophils into the airway, as well as enhanced nitric oxide generation in the airway. p53-deficient neutrophils displayed enhanced microbicidal function. Despite enhanced bacterial clearance, infected p53^{-/-} mice suffered increased mortality from pneumonia, likely due to aggravated lung injury from an overexuberant immune response.

Since p53-activating agents are widely used in human cancer therapy, the authors urge researchers to define the effects of pharmacologic activation of p53 on the human innate immune response in vivo. They also suggest that future studies should determine whether genetic polymorphisms leading to hypofunction of the p53 pathway are associated with increased risk for lung injury or mortality during human pneumonia. **(MM)**

Citation: Madenspacher JH, Azzam KM, Gowdy KM, Malcolm KC, Nick JA, Dixon D, Aloor JJ, Draper DW, Guardiola JJ, Shatz M, Menendez D, Lowe J, Lu J, Bushel P, Li L, Merrick BA, Resnick MA, Fessler MB.

(<http://www.ncbi.nlm.nih.gov/pubmed/23630228>)

2013. p53 integrates host defense and cell fate during bacterial pneumonia. *J Exp Med* 210(5):891-904.

Phenobarbital directly binds to EGFR to activate CAR in the liver

In a collaborative effort involving the Pharmacogenetics Section and the Computational Chemistry-Molecular Modeling Support Group, NIEHS scientists identified the mechanism by which the barbiturate phenobarbital activates the constitutive active androstane receptor (CAR). They demonstrated that phenobarbital directly binds to the epidermal growth factor receptor (EGFR) to block a signaling cascade that prevents CAR activation. Because of the potential widespread applicability of this mechanism of drug activation, these results could have broad implications for human health.

The researchers demonstrated that activation of the EGFR pathway prevented the dephosphorylation and activation of CAR in primary mouse hepatocytes. Using extensive biochemical techniques, they showed that the scaffold protein RACK1 plays a key role, acting as a mediator between EGFR and CAR. Further, through isothermal titration calorimetry, binding analyses, and molecular modeling, they revealed that phenobarbital directly binds to EGFR in a manner that inhibits its activation. Thus, phenobarbital activates CAR by blocking the inhibitory actions of EGFR on CAR.

This study has resolved an issue that has plagued the field of phenobarbital research for more than 50 years, by identifying EGFR as its receptor. It also provides novel insight as to how phenobarbital activates CAR to mediate its physiological actions. **(HF)**

Citation: Mutoh S, Sobhany M, Moore R, Perera L, Pedersen L, Sueyoshi T, Negishi M.

(<http://www.ncbi.nlm.nih.gov/pubmed/23652203>)

2013. Phenobarbital indirectly activates the constitutive active androstane receptor (CAR) by inhibition of epidermal growth factor receptor signaling. *Sci Signal* 6(274):ra31.

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