HelmholtzZentrum münchen
German Research Center for Environmental Health

Scientific Highlight April 2010

☐ co-ordinated with the Director of the Institute / Head of Department

Institute of Clinical Molecular Biology - Department of Molecular Epigenetics / Institute of Molecular Immunology

PSP-Element:
G-501400-001, G-501700-003

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Title of the Highlight:
The tumor suppressor p53 connects ribosome biogenesis to cell cycle control

Keywords:
ribosome biogenesis, cellular targets of chemotherapeutic drugs, cell cycle control

Central statement of the Highlight in one sentence:
Chemotherapeutic drugs activate the p53 tumor suppressor check point by inhibition of ribosome biogenesis

Text of the Highlight:

Since its first description more than 30 years ago p53 has become a paradigm for a protein with versatile functions. P53 sensitizes a large variety of genetic alterations and has been entitled the guardian of the genome. Stabilization of p53 upon DNA damage is accompanied by a complex pattern of modifications, which ascertain the cellular response either in the direction of a reversible or irreversible cell cycle arrest or programmed cell death. More recently it became evident that p53 also responds to non-genotoxic cell stress, in particular if ribosome biogenesis is affected.

In the two paper 2010 in the *Journal of Biological Chemistry* we describe the stabilization of the tumor suppressor p53 by non-genotoxic stress. P53 is stabilized if processing of the 18S or 28S ribosomal RNA is selectively inhibited by knockdown of specific processing factors, or if production of ribosomal RNA is inhibited by various chemotherapeutic drugs. Inhibition of ribosome biogenesis is accompanied by a G1 cell cycle arrest in p53+/+ cells, but not in p53-/- cells.

Publications:

Defects in 18S or 28S rRNA processing activate the p53 pathway. Hölzel, M., Orban, M., Hochstatter, J., Rohrmoser, M., Harasim, T., Malamoussi, A., Kremmer, E., Längst, G., and Eick, D. (2010) Journal of Biological Chemistry, 285,188-196

Chemotherapeutic drugs inhibit ribosome biogenesis at various levels. Burger, K., Mühl, B., Harasim, T., Rohrmoser, M., Malamoussi, A., Orban, M., Kellner, M., Gruber-Eber, A., Kremmer, E., Hölzel, M. and Eick, D. (2010) Journal of Biological Chemistry, in press

The tumor suppressor p53 connects ribosome biogenesis to cell cycle control: a double-edged sword. Hölzel, M., Burger, K., Mühl, B., Orban, M., Kellner, M., and Eick, D. (2010) Oncotarget, in press

Taking account of the HMGU mission:
The impact of environmental factors (here chemotherapeutic drugs) on cellular systems is of highest interest. Here we describe the process of ribosome biogenesis as molecular target of a large variety of chemotherapeutic drugs, which are currently successfully applied in clinical therapy regimens.

The internal HMGU co-operation partners with whom the Highlight was compiled, if appropriate:

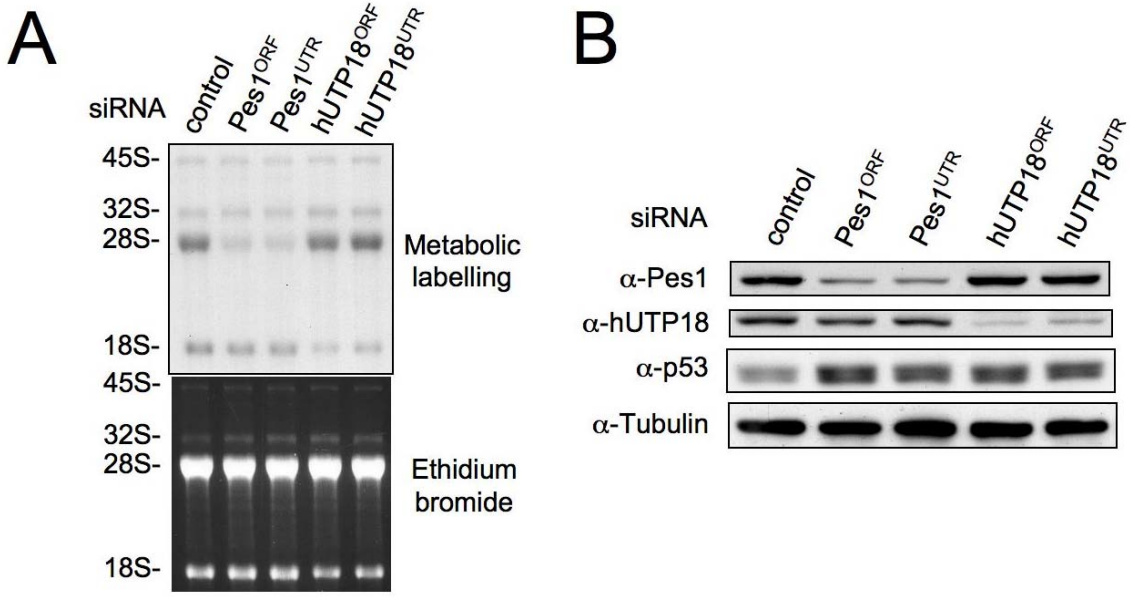
Institute of Molecular Immunology G-501700-003

The tumor suppressor p53 connects ribosome biogenesis to cell cycle control

Department of Molecular Epigenetics

Defects in 18S or 28S rRNA processing activate the p53 pathway

Hölzel, M., Orban, M., Hochstatter, J., Rohrmoser, M., Harasim, T., Malamoussi, A., Kremmer, E., Längst, G., and Eick, D. (2010) Journal of Biological Chemistry, 285,188-196



Depletion of hUTP18 or Pes1 induces accumulation of p53. *A.* 2fTGH cells were treated with Pes1 or hUTP18 siRNAs and a metabolic labelling of nascent ribosomal RNA was subsequently performed. *B.* Cells were treated as described in A and total cell lysates were harvested for Western blot analysis.

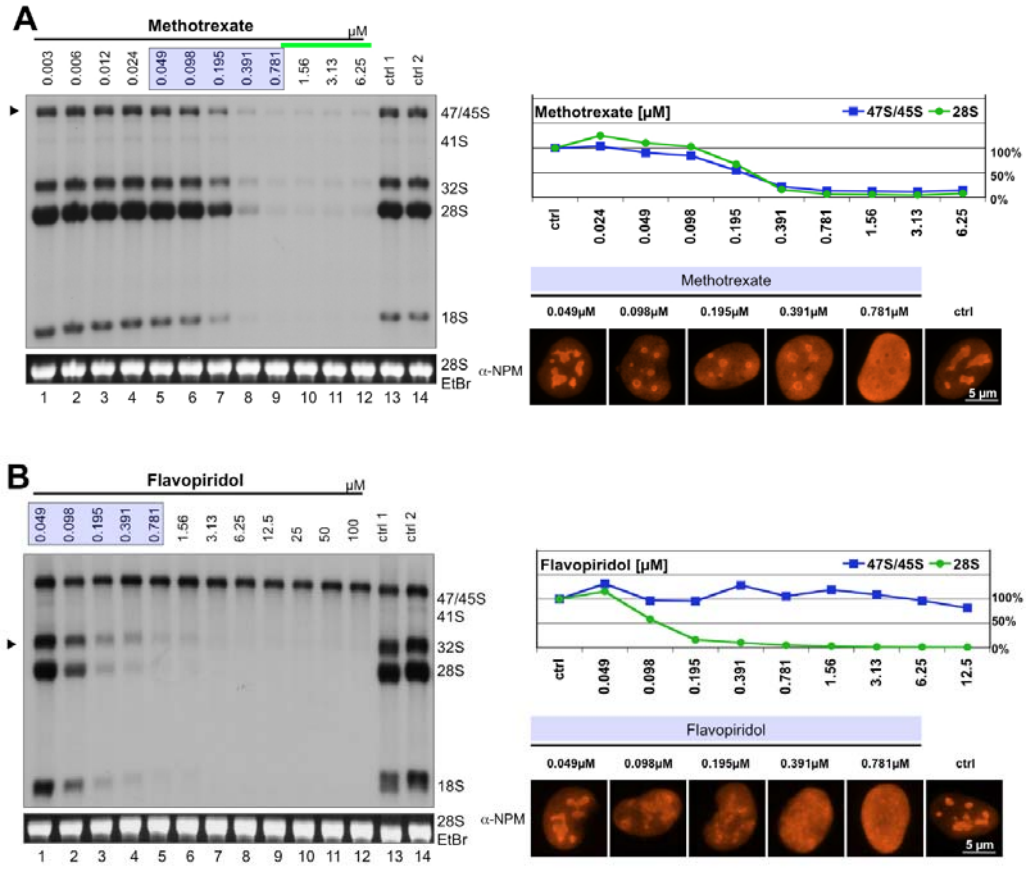
Conclusion: Inhibition of ribosome biogenesis at the level of 18S rRNA and 28S rRNA synthesis independently induce stabilization of the tumor suppressor p53

The tumor suppressor p53 connects ribosome biogenesis to cell cycle control

Department of Molecular Epigenetics

Chemotherapeutic drugs inhibit ribosome biogenesis at various levels

Burger, K., Mühl, B., Harasim, T., Rohrmoser, M., Malamoussi, A., Orban, M., Kellner, M., Gruber-Eber, A., Kremmer, E., Hölzel, M. and Eick, D. (2010) Journal of Biological Chemistry, in press



We determined the inhibitory concentration of 36 chemotherapeutic drugs for transcription and processing of ribosomal RNA by *in vivo* labeling experiments. Inhibitory drug concentrations were correlated to the loss of nucleolar integrity. Drugs inhibited ribosomal RNA synthesis either at the level of (A) rRNA transcription (e.g. Oxaliplatin, Doxorubicin, Mitoxantrone, Methotrexate), (B) early rRNA processing (e.g. Camptothecin, Flavopiridol, Roscovitine), or (C, not shown) late rRNA processing (e.g. 5-Fluorouracil, MG-132, Homoharringtonine). Blockage of rRNA transcription or early rRNA processing steps caused nucleolar disintegration (blue boxes), while blockage of late rRNA processing steps left the nucleolus intact (not shown).

Conclusion: Inhibition of ribosome biogenesis by chemotherapeutic drugs potentially contributes to the efficacy of therapeutic regimens.