Pathophysiological impact of targeting the ROS-p53 axis

Akademisk avhandling

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av

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Avhandlingen baseras på följande delarbeten:

I. Sayin VI, Nilton A, Ibrahim MX, Agren P, Larsson E, Petit MM, Hulten LM, Stahlman M, Johansson BR, Bergo MO and Lindahl P.
Zfp148 deficiency causes lung maturation defects and lethality in newborn mice that are rescued by deletion of p53 or antioxidant treatment
PLoS One **2013** *8(2):e55720*

II. Nilton A*, Sayin VI*, Bondjers C, Agren P, Bergo MO and Lindahl P
*Equal Contribution
Zfp148 deficiency reduces tumor formation in APCMin/+ mice in a p53-dependent manner *In Manuscript*

III. Sayin VI, Ibrahim MX, Larsson E, Nilsson JA, Lindahl P and Bergo MO.
Antioxidants accelerate lung cancer progression in mice
Science Translational Medicine **2014** *6(221):221ra15*

IV. Sayin VI, Khan OM, Pehlivanoglu LE, Staffas A, Ibrahim MX, Asplund A, Agren P, Nilton A, Bergström G, Bergo MO, Borén J and Lindahl P.
Loss of one copy of Zfp148 reduces lesional macrophage proliferation and atherosclerosis in mice by activating p53
Circulation Research **2014** *115(9):781-9*

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ABSTRACT

Pathophysiological impact of targeting the ROS-p53 axis

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The goal of this PhD thesis was to define the importance of the interplay between reactive oxygen species (ROS) and their activation of the tumor suppressor p53 in development and disease. We addressed this question using molecular biology and biochemical techniques together with mouse genetics and bioinformatics.

We have made two important discoveries:

First, we show that antioxidant supplementation accelerates lung cancer progression in mice and the growth of human lung cancer cell lines. By reducing the levels of ROS and DNA damage, antioxidants deactivate the p53 protein and help cancer cells to evade growth arrest.

Second, we show that the transcription factor zinc finger protein 148 (Zfp148) is a potent suppressor of p53 activation under oxidative conditions. During lung development, suppression of p53 prevents growth arrest of pulmonary cells and permits prenatal lung maturation. However, in the $Apc^{Min/+}$ model of colorectal cancer and in the $Apoe^{-/-}$ model of atherosclerosis, suppression of p53 promotes tumor development and atherosclerosis, respectively. Thus Zfp148 suppression of p53 plays important roles in both physiological and pathological contexts.

We conclude that:

1) Antioxidant supplementation may stimulate the growth and progression of undiagnosed lung tumors and should be used with caution. The risk of developing lung cancer in patients with chronic obstructive pulmonary disease (COPD) who take the antioxidant acetylcysteine to break down mucus should be carefully evaluated.

2) Therapeutic targeting of Zfp148 may have beneficial effects in cancer and atherosclerosis by increasing p53 activity.

Keywords: ROS, p53, Antioxidants, Zfp148, cancer and atherosclerosis

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