Adiposity - GRIM1/NIR

Target for the Treatment of Disturbances of Skeletal Muscle and Fat Cell Differentiation

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Technology

The therapeutic modification of the function of GRIM1/NIR may counteract premature muscle degeneration or actively intervene in processes which build up muscle. Furthermore GRIM1/NIR shows a sub-nuclear relocalization during adipocyte differentiation. This technology further relates to antibodies which specifically bind to an epitope of GRIM1/NIR. Monoclonal humanized antibodies of this type can be employed in therapy. An alternative area of use of these antibodies is diagnosis. Furthermore this invention relates to a method for identifying substances which influence the biological function of GRIM1/NIR. It is possible with this test system to identify substances which interact with the GRIM1/NIR polypeptide and inhibit or enhance the biological function of GRIM1/NIR.

Innovation

- Humanized monoclonal antibodies for therapy or polyclonal antibodies for diagnostic of
  - degenerative muscle disorders
  - disturbances in fat cell differentiations

Application

- Degenerative muscle disorders
- Controlling muscle atrophy in the aging man
- Controlling of fat cell differentiations, e.g. in case of adipositas

Market Potential

- Muscular atrophy affects a major number of elderly people. Muscular atrophy decreases quality of life as the sufferer becomes unable to perform certain tasks or worsen the risks of accidents while performing those.
- 30% of the US population and 20% of the European population are considered to be obese.

Responsible Scientist

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Patent Status

Filed (PRD) March 20th 2002

Reference Number

ZEE20010713b

Status: Aug-11

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Control of adipogenesis by the signal-regulated INHAT-repressor NIR

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Summary:
To initiate the functional characterization of NIR during development and organogenesis, we applied a tandem affinity purification (TAP) strategy combined with mass spectrometry (MALDI-TOF) to identify NIR-interacting partners such as the tumour suppressor p53 (Hublitz et al., 2005). Association of p53 and NIR was verified in vitro and in vivo. Upon recruitment by p53, NIR represses transcription of both p53-dependent reporters and endogenous target genes. Knockdown of NIR by RNA interference significantly enhances acetylation of histones at p53-regulated promoters. Moreover, p53-dependent apoptosis is robustly increased upon depletion of NIR. In summary, our findings describe NIR as a novel INHAT that plays an important role in the control of p53 function.

The TAP approach revealed also several other NIR-interacting proteins such as FAD24, neuroguidin, peter pan, and PES1, that are described to play important role in adipogenesis (Tominaga et al., 2004; Jung et al., 2006; Suarez-Huerta et al., 2000; Lapik et al., 2004). Importantly, by bioinformatic data mining of the yeast (Gavin et al., 2006) and C. elegans proteome (Zhong et al., 2006), respectively we uncovered that Noc2p, the yeast and worm homologs of NIR, form a complex with the respective homologs of FAD24, Neuroguidin, peter pan, and PES1. Thus, this NIR associated complex in evolutionary conserved. In addition, MacKay et al. 2003 showed that in C. elegans lpd-2 (neuroguidin homolog), lpd-6 (peter pan homolog), and lpd-7 (PES1 homolog) are required for fat storage. Finally, a genome-wide RNAi analysis of C. elegans revealed that knockdown of the NIR homolog Pro-2 results in a "fat-reduced" phenotype (Ashrafi et al., 2003). The physical interaction between FAD24, neuroguidin, peter pan, PES1, and NIR was confirmed in vitro and in vivo. Moreover, we could show direct interaction between NIR and GSK3β, a key regulator in adipocyte differentiation (Ross et al., 2000). In vitro, NIR is a substrate for GSK3β-mediated phosphorylation, implicating NIR function in Wnt signalling. Finally, miRNA-mediated knockdown of NIR severely impairs adipogenesis in mammalian cells. In summary, these data suggest a physiological role of NIR in adipogenesis.

Publications: