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Bad Boy with a Twist: Targeting the 37 kDa/67 kDa Laminin Receptor for Treatment of Cancer and Neurodegenerative Diseases and for Changing Telomere Dynamics

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Editorial

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Not many receptors are as multifunctional as the 37kDa/67kDa laminin receptor (LRP/LR) [1,2]. Is LRP/LR the black sheep, the "bad boy", the one who promotes cancer, prion disorders, Alzheimer's disease, bacterial, viral and parasite infections? [1,2]. Indeed, LRP/LR, also known as LAMR, ribosomal protein SA (RPSA) or p40, acts as the receptor for the cellular and infectious prion proteins PrPc [3] and PrPSc [4] respectively, and promotes prion propagation in vitro and in vivo, processes which can be impeded by LRP/LR specific antibodies and siRNA mediated knock-down of LRP [5]. In particular, passive immune-transfer of a LRP/LR specific antibody (W3) into Scrapie-infected mice resulted in a significant reduction of the peripheral prion propagation and prolonged survival of the mice [6]. Targeting LRP/LR might therefore be a therapeutic option for human prion disorders such as Creutzfeldt-Jakob Disease. LRP/LR also serves as a receptor for amyloid-beta (A-beta) and promotes A-beta shedding contributing to neurotoxicity in Alzheimer's disease [1]. LRP specific antibodies and shRNAs directed against LRP mRNA were both efficient in impeding A-beta induced cytotoxicity [1,2]. Interestingly, the prion protein PrPc is necessary for the rescuing effect of LRP/LR specific antibodies on A-beta induced cytotoxicity [7]. These findings recommend LRP/LR specific antibodies and siRNAs as alternative powerful therapeutics for Alzheimer's disease.

Cancer undergoes metastasis, impedes apoptosis and turns angiogenesis into tumor angiogenesis for excessive nutrient and oxygen delivery to neoplastic tissues. LRP/LR, at normal levels, is beneficial for the organism via binding extracellular matrix proteins, such as laminin-1, which contributes to cell proliferation, movement and growth [2,1]. The "receptor" has also been found in the cytosol supporting translational processes through ribosome binding capabilities as well as the nucleus encompassing maintenance of nuclear structures through interactions with histones [1]. LRP/LR further contributes to the cytoskeleton, the development, differentiation and tissue responses [2]. The observed increased level of LRP/LR in neoplastic tissues promotes adhesive and invasive processes, key components for metastasis, impedes apoptosis and promotes tumor angiogenesis [1]. In this manner LRP/LR seems to contribute to numerous if not all cancer types. The LRP specific antibody (IgG1-iS18) was efficient in blocking adhesive and invasive processes resulting in the impediment of metastasis in a variety of cancer cells including: fibrosarcoma, lung, cervical, prostate, breast, oesophageal, liver [1], pancreatic, neuroblastoma [8], early and late stage colorectal carcinoma [9] as well as melanoma cells [10]. A polyclonal LRP/LR specific antibody (W3) blocked angiogenesis in HUVE cells [11] and LRP knock-down impeded apoptosis in lung, cervical [12] breast as well as oesophageal cancer cells [13].

That's good news and recommending LRP/LR specific antibodies and siRNAs as potential powerful alternative drugs for treatment of patients suffering from various cancer types, especially if the drugs are administered in combination. The LRP/LR based treatments may be advantageous over conventional therapeutics on the market, such as Herceptin®, approved for breast and gastric cancer (http://www.herceptin.com/) since they may target a variety of (if not all) cancer types. Cancer extends its pestilent potential on uncontrolled cell proliferation and metastasis through activation of telomerase, which maintain and stabilize telomeres at chromosome ends preventing them from degradation and illegitimate processing [14].

Now the bad boy comes in to play again by co-localizing and interacting with the human telomerase reverse transcriptase (hTERT), at least in tumorigenic breast cancer cells [15]. siRNA mediated knock-down of LRP/LR by siRNA technology significantly reduced telomerase activity [15], suggesting that LRP/LR extends its pro-tumorigenic activities by supporting telomerase stability and maintenance of uncontrolled cell proliferation. Now, when it comes to ageing, the bad boy may twist and turn into an angel to keep forever young. Elongation of telomeres, catalysed by telomerase, is considered as one of the most critical processes for impeding the ageing process [14]. LRP/LR therefore might have the potential to act as an alternative powerful anti-ageing drug through telomerase activation and telomere maintenance, which may bear a risk of turning normal cells into proliferating cells with a neoplastic component. This risk, however, seems to be minimal since introduction of hTERT was sufficient to immortalise cells without any risk of tumorigenic onset [16].

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