ANGIOGENESIS

Familiar faces and new connections

DOI:
10.1038/nrd2160

> PML levels in human cancer might serve as a biological marker to predict efficacy of treatment with mTOR or angiogenesis inhibitors.

The well-known tumour-suppressor gene promyelocytic leukaemia (PML) is downregulated in a wide range of human cancers. Reporting in *Nature*, Bernardi *et al.* have discovered a new facet of PML function, and show that it acts as a crucial inhibitor of neo-angiogenesis, in both neoplastic and ischaemic conditions. This has important prognostic implications, and could pave the way for the development of innovative therapeutic strategies.

To date, the tumour-suppressive function of PML has mainly been attributed to its regulation of tumour-suppressive transcription factors, such as p53, retinoblastoma and SMAD. Now it seems that PML exerts some of its tumour-suppressive role by controlling the 'angiogenic switch' — an essential process in tumorigenesis that is often induced in response to intra-tumoural hypoxia.

Using PML-deficient mice and $PML^{-/-}$ mouse endothelial fibroblast cells (MEFs), as well as a model for ischaemic revascularization and *in vivo* and in *vitro* tumorigenesis assays, the authors managed to unravel the molecular mechanisms underlying this process. They found that PML regulates angiogenesis by downregulating the rate of synthesis of the transcription factor hypoxia-inducible factor 1α (HIF1α), which, in turn, regulates the transcription the pro-angiogenic secreted protein vascular endothelial growth factor (VEGF). $PML^{-/-}$ mice were found to recover much faster from ischaemia as a result of enhanced recruitment of circulating endothelial progenitor cells from the bone marrow, a process largely mediated by VEGF. Conversely, in wild-type mice, PML levels increased after ischaemia, and HIF1α-mediated transactivation was repressed by PML in a dose-dependent manner. Interestingly, although HIF1α is known to be tightly controlled by oxygen levels that regulate its degradation, PML was found to negatively regulate the synthesis of HIF1α.

Digging further into the molecular details of this regulation, the authors found that PML, under hypoxic conditions, acts as a negative regulator of HIF1α by repressing the kinase mammalian target of rapamycin (mTOR) through a novel mechanism. PML was found to physically interact with mTOR, leading to nuclear accumulation of mTOR and preventing mTOR interacting with the small GTPase Rheb. In the context of cancer, this has interesting consequences — although $PML^{-/-}$ tumours were found to be larger and to have a greater microvessel density, they were also found to be more sensitive to mTOR inhibition by rapamycin, and more sensitive to a monoclonal antibody that inhibits tumour angiogenesis.

These findings have important prognostic and therapeutic implications for the treatment of ischaemic conditions and cancer. PML levels

in human cancer might serve as a biological marker to predict efficacy of treatment with mTOR or angiogenesis inhibitors, and new cancer combination therapies can be devised such that drugs known to upregulate PML protein and mRNA levels (such as proteasome inhibitors and interferons) are used with angiogenesis inhibitors or mTOR inhibitors. Conversely, drugs that are known to reduce PML protein levels, such as low doses of As_2O_3, could be formulated for the treatment of acute ischaemic conditions.

Alexandra Flemming

ORIGINAL RESEARCH PAPER Bernardi, R. *et al.* PML inhibits HIF-1α translation and neoangiogenesis through repression of mTOR. *Nature* **442**, 779–785 (2006)