

preproGRP transcripts were found in 28% of the blood samples. The detection of a hematogenic tumor cell spread with preproGRP in MTC correlated significantly with advanced tumor categories. CK20 transcripts were detected in 75% of the blood samples of patients with thyroid carcinoma and distant metastases. Moreover disseminated tumor cells were detected in 21% of the bone marrow samples with CK20-PCR and 13% with preproGRP (only for MTC).

Conclusion: Both assays are sensitive enough to detect disseminated thyroid carcinoma cells in blood and bone marrow samples. However, the prognostic relevance of these disseminated tumor cells is not completely understood and has to be addressed in further investigations.

doi:10.1016/j.ejcsup.2006.04.052

S52. Pdc4 TARGETS eIF4A TO INHIBIT TRANSLATION, TRANSCRIPTION, TUMORIGENESIS, AND INVASION

Nancy H. Colburn, Hsin-Sheng Yang, Aaron Jansen. Laboratory of Cancer Prevention, National Cancer Institute, Frederick, MD 21702, USA.

Despite its name, Programmed Cell Death 4 (Pdc4) may or may not induce apoptosis. Pdc4 was discovered as a highly expressed gene in mouse JB6 cells resistant to transformation. Pdc4 inhibits transformation and tumorigenesis, in part by specifically inhibiting AP-1 dependent transcription. The binding partners of Pdc4 are not Jun or Fos proteins but are translation initiation factors eIF4A and eIF4G. Pdc4 inhibits translation initiation by directly binding to translation initiation factor eIF4A and inhibiting its helicase activity. The helicase activity of eIF4A is important for unwinding 5'UTR structured mRNAs prior to scanning to the translational start site. Pdc4 also interferes with scaffold eIF4G function. Pdc4 must interact with eIF4A and inhibit translation in order to inhibit AP-1 transactivation, as Pdc4 mutants inactivated for eIF4A binding fail to inhibit AP-1. Recent findings with K14-driven Pdc4 expression in mice have established that Pdc4 inhibits translation of a 5'UTR-structured mRNA as well as expression of "translationally repressed" proteins. Pdc4 inhibits AP-1 dependent transcription and acts to attenuate papilloma-metaplasia and papilloma to carcinoma conversion. Moreover Pdc4 expression (a) is downregulated with progression in several human cancer sites, (b) confers sensitivity to certain therapeutic drugs, and (c) suppresses invasion and motility in human cancer cell lines. Pdc4 suppresses cancer cell invasion by targeting the expression of MAP4K1, an upstream regulator of Jun N-terminal Kinase signaling, with consequent inhibition of AP-1 dependent transcription. Thus, activating or mimicking the expression of Pdc4 might be an attractive preventive or therapeutic strategy. Enhancing the interaction of Pdc4 with eIF4A or targeting downstream translational targets may produce the "desired" but not the "undesired" outcomes achieved with mTOR inhibitors. mTOR inhibitors repress translation by enhancing the interaction of 4E-BP with cap binding protein eIF4E but are also immunosuppressive. Pdc4 appears not to show immunosuppressive activity. Although we and others have identified translationally repressed candidates, the functionally significant translational targets of

Pdc4 are still unknown. Knowing these Pdc4 targets is important for designing prevention strategies. In summary, Pdc4 is the first suppressor of tumorigenesis and invasion known to directly inhibit translation initiation. Translation initiation thus appears to be a promising molecular target for cancer prevention and intervention.

FURTHER READING

1. Cmarik, J. L., Min, H., Hegamyer, G., Zhan, S., Kulesz-Martin, M., Yoshinaga, H., et al. Differentially expressed protein Pdc4 inhibits tumor promoter-induced neoplastic transformation. *Proc Natl Acad Sci USA*, 96(24), 14037-14042.
2. Yang, H. S., Jansen, A. P., Komar, A. A., Zheng, X., Merrick, W. C., Costes, S., et al. The transformation suppressor Pdc4 is a novel eukaryotic translation initiation factor 4A binding protein that inhibits translation. *Mol Cell Biol*, 23(1), 26-37.
3. Yang, H. S., Cho, M. H., Zakowicz, H., Hegamyer, G., Sonenberg, N., & Colburn, N. H.. A novel function of the MA-3 domains in transformation and translation suppressor Pdc4 is essential for its binding to eukaryotic translation initiation factor 4A. *Mol Cell Biol*, 24(9), 3894-3906.
4. Yang, H.-S., Matthews, C. P., Clair, T., Wang, Q., Baker, A. R., Li, C.-C., et al. Tumorigenesis suppressor Pdc4 down-regulates MAP4K1 expression to suppress colon carcinoma cell invasion. *Mol Cell Biol*, 26(4), 1297-1306.
5. Jansen, A. P., Camalier, C. E., Stark, C., & Colburn, N. H.. Characterization of programmed cell death 4 in multiple human cancers reveals a novel enhancer of drug sensitivity. *Mol Cancer Ther*, 3(2), 103-110.
6. Jansen, A. P., Camalier, C. E., & Colburn, N. H.. Epidermal expression of the translation inhibitor programmed cell death 4 suppresses tumorigenesis. *Cancer Res*, 65(14), 6034-6041.

doi:10.1016/j.ejcsup.2006.04.053

S53. THE ISEL AND BR21 TRIALS - OUTCOMES SIMILAR OR DIFFERENT?

Nick Thatcher. Christie Hospital, Manchester, UK.

The survival effects of EGFR-TKI therapy have been evaluated in two Phase III placebo-controlled studies in refractory NSCLC: ISEL (IRESSA Survival Evaluation in Lung cancer no. = 1692) and BR21 (erlotinib no. = 731).^{1,2} Gefitinib (Iressa) showed some improvement in survival compared with placebo, but the difference did not reach statistical significance on the prespecified stratified log rank test required for registration in either the overall population (HR 0.89; $p = 0.087$; median 5.6 vs. 5.1 months) or in patients with adenocarcinoma (HR 0.84; $p = 0.089$; median 6.3 vs. 5.4 months). However, preplanned subgroup analyses showed that gefitinib significantly prolonged survival in patients of Asian ethnicity and in patients who had never smoked. The erlotinib BR21 study had a similar design to ISEL, but demonstrated a statistically significant overall survival benefit for erlotinib HR = 0.7 $p < 0.001$ median 6.7 vs. 4.7 months.² However the 95% confidence intervals for the HRs overlap ISEL 0.77-1.02 and 0.58-0.85 for BR21