MacroH2A1.1, a new epigenetic target for treatment of prostate cancer.

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Purpose:
The principal mechanisms leading to cancer not only result from genetic defects but also from epigenetic modifications.
The histone variant macroH2A1.1 is implicated in a variety of pathological processes including tumor development [1-6], and stem cell reprogramming [7,8], but its precise genomic distribution and role remain unknown [9].
To elucidate the role of macroH2A1.1 in cancer, we analyzed the tumorigenic and metastatic potential of androgen receptor-negative prostate carcinoma cells (PC-3) after inducible RNAi-mediated knockdown of macroH2A1.1 in an orthotopic tumor mouse model.

Experimental Design:
PC-3 expressing both luciferase and a fluorescent reporter were transduced with an inducible lentivector for shRNA expression directed either against macroH2A1.1 RNA (macro_shRNA) or against an irrelevant RNA sequence (control_shRNA).
Macro_shRNA and control_shRNA cells were inoculated orthotopically into the dorsal prostatic lobe of immunocompromised NMRI/Nu mice.
Primary tumor growth was monitored over time by non-invasive luminescence, and metastasis was evaluated at week 6 by fluorescence.
Effects of MacroH2A1.1 knock-down were compared to those of the reference compound, Docetaxel. Docetaxel (20 mg/kg, i.p).or its vehicle was injected once a week starting from week 3.

Results:
In vitro, induced macroH2A1.1 knock-down resulted in down-regulation of macroH2A1.1 protein levels by about 50%.
In vivo, compared to vehicle, primary tumor growth was reduced in docetaxel group and in macro_shRNA group (p< 0.01).
Decrease of draining and distant lymph nodes fluorescence (metastases) was observed with macro_shRNA relative to control_shRNA, although effect did not reach significance. On the opposite, macro_shRNA had no effect on LN metastasis incidence.
Notably, docetaxel treatment and macroH2A1.1 silencing resulted in significant reduction of lung metastasis as compared to their respective controls (p<0.05).

Conclusion:
Knock-down of the histone variant macroH2A1.1 decreases tumorigenicity and drastically limits tumor dissemination in a spontaneous metastasis xenograft model of human PCa. In particular, macroH2A1.1-
depletion specifically abrogated dissemination into the lung. This finding might reflect a potential role of macroH2A1.1 in cellular plasticity required for the establishment and/or development of metastasis.

In conclusion, macroH2A1.1 is a promising epigenetic target for treatment of prostate cancer and for the development of a novel class of epi-drugs targeting circulating tumor cells.

References: