Amplification and overexpression of vinculin are associated with increased tumour cell proliferation and progression in advanced prostate cancer

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Author(s) Ruiz, Christian; Holz, David R; Oeggerli, Martin; Schneider, Sandra; Gonzales, Irma M; Kiefer, Jeffrey M; Zellweger, Tobias; Bachmann, Alexander; Koivisto, Pasi A; Helin, Heikki J; Mousses, Spyro; Barrett, Michael T; Azorsa, David O; Bubendorf, Lukas
Author(s) at UniBasel Bachmann, Alexander ; Bubendorf, Lukas ; Zellweger, Tobias ;
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Androgen withdrawal is the standard treatment for advanced prostate cancer. Although this therapy is initially effective, nearly all prostate cancers become refractory to it. Approximately 15% of these castration-resistant prostate cancers harbour a genomic amplification at 10q22. The aim of this study was to explore the structure of the 10q22 amplicon and to determine the major driving genes. Application of high-resolution array-CGH using the 244k Agilent microarrays to cell lines with 10q22 amplification allowed us to narrow down the common amplified region to a region of 5.8 megabases. We silenced each of the genes of this region by an RNAi screen in the prostate cancer cell lines PC-3 and 22Rv1. We selected genes with a significant growth reduction in the 10q22 amplified cell line PC-3, but not in the non-amplified 22Rv1 cells, as putative target genes of this amplicon. Immunohistochemical analysis of the protein expression of these candidate genes on a tissue microarray enriched for 10q22 amplified prostate cancers revealed vinculin as the most promising target of this amplicon. We found a strong association between vinculin gene amplification and overexpression ($p < 0.001$). Further analysis of 443 specimens from across all stages of prostate cancer progression showed that vinculin expression was highest in castration-resistant prostate cancers, but negative or very low in benign prostatic hyperplasia ($p < 0.0001$). Additionally, high tumour cell proliferation measured by Ki67 expression was significantly associated with high vinculin expression in prostate cancer ($p < 0.0001$). Our data suggest that vinculin is a major driving gene of the 10q22 amplification in prostate cancer and that vinculin overexpression might contribute to prostate cancer progression by enhancing tumour cell proliferation.
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