

A Prominent Couple

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Valorisation

Valorisation in its original sense means the creation of economic value. In biomedical research, valorisation aims to assess the contribution of scientific knowledge to industrial activities and its application as potential products or services with societal benefit. This chapter is meant to position the scientific results from the preceding chapters in the context of social utilisation and to generate potential health care returns in appreciation of public investments.

Social relevance

Getting the diagnosis of 'cancer' is a significant and dramatic incident for patients and their relatives. Prostate cancer (PCa) frequently shows an indolent clinical course with a 2.5-3% lifetime risk of dying from progressive disease [1]. However, risk stratification remains a major clinical question. Since clinicopathologic criteria are insufficient to efficiently distinguish between indolent and aggressive tumors, patients experience uncertainty about the risk of disease progression, which means an additional burden to them. Knowledge about the molecular profiles of an individual tumor and its potential to progress could provide clinicians with valuable information about the clinical course and support treatment recommendations. Proper counseling and involvement in therapy planning, especially of patients that could be considered for conservative management, positively affects patient's satisfaction after treatment [2]. Reducing over-treatment of patients with insignificant disease on the one hand would decrease comorbidity as a consequence of the PCa treatment, such as a surgical procedure, with benefit for the quality of life and reduction of health care costs. The accurate selection of patients that need aggressive treatment on the other hand would improve prognosis by avoiding a delay until initiation of a potentially effective treatment.

Scientific and clinical relevance

PCa is the most prevalent non-cutaneous malignancy accounting for 15% of the cancers diagnosed in men [3]. Depending on risk estimation, different treatment options are possible. During the decision-making process towards radical treatment versus conservative management, clinicians use various prediction tools to determine patients that are at increased risk for disease progression. Those tools are based on clinicopathologic variables. However, PCa is a genomically complex disease. The molecular mechanisms and implications for clinical outcome of distinct genomic aberrations are yet poorly understood. Identification of the molecular profiles that promote aggressive tumor biology is therefore essential to support the prediction of progressive disease, and to recommend aggressive treatment to patients that will most likely benefit from it.

In the studies compiled in this doctoral thesis, novel targets have been identified that provide insights into the molecular mechanisms of *TMPRSS2:ERG* fusion-positive PCa. Defining tumors by their individual genetic constitution, rather than histopathological patterns could lead to more accurate risk stratification.

Detection of the *TMPRSS2:ERG* gene fusion has currently no prognostic or therapeutic implications in routine clinical management. Determination of the gene fusion status could direct the selection of patients for clinical trials that are most likely to benefit from a molecularly targeted therapy reducing the number of required patients to randomize and potentially increasing the chance of success of drug effectiveness testing (*targeted design*). This could further create an economically valuable strategy to control public investments into scientific research.

We suggest that the TGF- β -ALK1 receptor-mediated signaling pathway in *TMPRSS2:ERG* positive tumors could be a promising candidate for future evaluation as therapy target in PCa. However, targeted therapy approaches are vulnerable to intrinsic resistance due to redundancy in signaling pathways in cancer cells [4]. Since ERG-mediated signaling deployed a second route, the FZD4-WNT signaling pathway, inhibition of both pathways could be considered as a combined concept to inhibit tumor activity. The identification of the two molecular determinants of epithelial-to-mesenchymal transition (EMT) in *TMPRSS2:ERG* positive tumors is therefore promising basis for future therapeutic approaches.

Recognition of therapy resistance is important to avoid disease progression. Functional characterization of biological processes involved in therapy resistance could identify novel targets to improve clinical management. *INSM1* was identified as promising regulator of a neuroendocrine (NE) phenotype in PCa cells. The power of *INSM1* lies in its specific overexpression in NE tumors. Since prostate cancers with NE characteristics are less likely to respond to hormonal agents, detection of *INSM1* overexpression could be valuable in counseling patients towards a chemotherapeutic treatment or enrolment in a clinical trial [5].

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