Editorial Commentary

N-Myc a key gene promoting a worst prostate cancer progression

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Prostate cancer is a lethal disease and despite several treatments available prognosis of patients with metastatic castration resistant prostate cancer (mCRPC) still remain poor.

Natural clinical history of the disease generally involves a phase of hormone-sensitive prostate cancer followed by the inexorable acquisition of resistance to androgen deprivation therapy. MCRPC is a clinical disease associated to resistance to androgen deprivation and other treatment approaches are required for its management. These mainly include: chemotherapy and new hormonal agents able to exercise a more effective hormone-production inhibition.

Despite these approaches, after variable time, prostate cancer cells develop resistance to systemic.

The clinical history of prostate cancer is strictly associated to a large time-heterogeneity in terms of genomic profile of tumour cells. Systemic treatment exercise, an external pressure which progressively leads to cancer cells evolution and acquisition of novel genomic alterations.

One of the most impressive changes could be observed in a transition of prostate cancer cells in a neuroendocrine phenotype, which is associated to poor clinical outcomes.

Berger *et al.* have carried out a further characterization of molecular models employed by cancer cells to escape from these external pressures in a recent study (1).

Briefly they proposed a mechanism by which N-Myc overexpression may leads to important epigenetic and transcriptomic reprogramming leading to acquisition of castration resistant status and evolution to neuroendocrine prostate cancer. Of interest, the identification of this alteration in addition to a specific molecular signature could help clinicians to early identify tumours more likely to evolve to NEPC (1). This would leads to development of personalized strategies in terms of clinical monitoring in course of therapy and early inclusion of these patients in clinical trials at time of progression.

Molecular mechanisms related to androgen and hormone inhibition resistance is a key and still not well-understood issue in prostate cancer (2,3).

There are several mechanisms proposed as primary driver of hormone resistance.

One of the most assessed mechanisms consisted on the production of slice variants of the androgen receptor (AR) (4,5). Normally AD is a ligand-dependent receptor able to promote gene transcription after dihydrotestosterone or testosterone binding. Alternative splicing of AR may lead to the development to different molecular structures of this receptors. Sometime these alternative structures may be directly active promoting transcription of target genes regardless the presence of natural ligand. As known AR-V7, AR-V12 are the most assessed splice variants associated to constitutional activity and hormone-inhibition resistance (4,5).

The presence of restored AR signalling due to AR-activating mutations, AR active splice variants, intra-tumoral production of androgen compounds are also mechanisms by which prostate cancer cells may acquire resistance to systemic hormonal treatments (4,5).

Epigenetic modifications are another mechanism proposed to overcome hormonal inhibition. Several genes showed an altered methylation compared to normal prostate tissue including: *SCGB3A1*, *HIF3A*, *AOX1*, *P115*, *ALKBH5*, *ATP11A*, *FHAD1*, *KLHL8*, *FLNC*, *EFS*, *ECRG4*, *PITX2*, *PDLIM4* and *KCMA1* (6-8). Altered methylation

strictly depends by altered activity of specific enzymes that belong to the family of DNA-methyltransferase. Also, modification of histones is involved in development of castration resistant status. Indeed, modifications of histone molecular conformations significantly modify accessibility of chromatin to transcription (6-8). The enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase enzyme of the Polycomb Repressive Coplex 2 (PRC2) which is strictly related to repression of several genes able to inhibit cell proliferation including *p53*. There is a known supposed association between EZH2 hyper-expression and development of more aggressive tumour phenotype (9-12).

In the already cited article of Berger *et al.* there was a confirmation of previously observations which suggested a strictly interaction between N-Myx and EZH2. In absence of EZH2 cells up-regulated genes, which were down-regulated by N-Myc (1).

EZH2 inhibitors are under investigation in combination with abiraterone and enzalutamide (NCT03480646) or with AR antagonist (NCT03741712) as there are strong evidences supporting a restored androgen response mediated by EZH2 inactivation.

Other promising strategies to overcome hormonal resistance are under investigation (13).

These involve: the adoption of histone deacetylase inhibitors, the use of PI3K-AKT-mTOR inhibitors, cyclins inhibitors and BET inhibitors (14,15).

Of these inhibitors of the bromodomain and extra terminal (BET) family proteins and bromodomain-containing proteins are of particular interest. Indeed these proteins are able to modulate the recruitment of other proteins modifying DNA transcription. Further evidences show that different BRD are able to interact with AR in the nucleus and mediate AR target genes transcription (14,15).

PI3K-AKT-mTOR pathway is strictly related to AR. Indeed through down-regulation of PHLPP in course of AR inhibition the PI3K pathway could be restored. Furthermore, loss of PTEN is associated to PI3K-AKT-mTOR pathway promotion and to development of CRPC (16,17). Thus, the association of inhibitor of PI3K-mTOR is a promising approach in the management of advanced MCRPC and several trials are ongoing (NCT03072238, NCT02121639).

In conclusion studies able to reveal novel insights about molecular altered pathways in prostate cancer are a critical issue. The novel evidences which correlate N-Myc to the development of more aggressive prostate tumors and in particular to cancer with neuroendocrine phenotype is of particular interest.

The attractive possibility to early identify tumours more likely to progress, as neuroendocrine subtypes should be further investigated. In particular, the more and more early administration of new hormonal compounds as well as the possibility to include these patients in clinical trials should justify the development of translational studies aimed to further investigate this issue (18).

Another issue that should be assessed is the alteration of N-Myc in a particular clinical setting composed of patients with metastatic hormone sensitive prostate cancer (mHSPC), which are known to be associated to worst clinical outcomes despite an increasing availability of active and effective systemic treatments.

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