From DNA binding to metabolic control: integration of -omics data reveals drug targets for prostate cancer

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Androgen signalling via the androgen receptor plays a critical role in prostate cancer development and is the primary drug target for prostate cancer therapy. However, given the frequent development of resistance to current therapies in many tumours, there is a great need for the identification of additional factors that could be exploited as drug targets. In this issue of *The EMBO Journal*, Massie *et al* (2011) have employed an integrated approach to reveal a role of androgen signalling in regulating central metabolism and molecular biosynthesis in prostate cancers. This study highlights how integrating various -omics data and combining these with clinical observations can bring new dimensions to our understanding of important clinical challenges and identification of novel drug targets.

Complexity is fundamental to biology, with most biological processes constituting multi-level dynamic complex systems involving interacting macromolecules such as DNA, RNAs, proteins and metabolites (Vidal, 2009). The repertoires of molecules constituting a biological process are regulated at multiple levels, including transcription, translation, protein modification, as well as according to metabolic state. Thus, the integration of information obtained from diverse experimental approaches is essential for our understanding of biological processes (Hawkins *et al*, 2010). The advancement of high-throughput -omics technologies (genomics, transcriptomics, proteomics, metabolomics and beyond) and asso-

ciated genome-wide data at different molecular levels (the genome, the transcriptome, the proteome, and the metabolome) in the same biological sample has provided a wealth of data for researchers. However, the large amount of information obtained from these high-throughput technologies and the exploitation of diverse technology platforms raise challenges in data processing and integration, and ultimately in obtaining a working hypothesis for further validation (Joyce and Palsson, 2006). Here, Massie *et al* (2011) approach this challenge and provide an example of how data from various -omics technologies can be integrated to provide an improved understanding of important clinical challenges and novel drug targets. The results highlight the role of androgen signaling in supporting prostate cancer development by regulating central metabolism and macromolecular biosynthesis. Moreover, the work identifies a putative drug candidate for prostate cancer.

Androgen receptor (AR) signalling is required for prostate development and normal prostate function. Furthermore, AR is involved in the development and progression of both androgen-dependent and castrate-resistant (androgen-independent) prostate cancer (Heinlein and Chang, 2004). Endocrine therapy with AR antagonists constitutes the first-line therapy for androgen-dependent prostate cancer. However, many tumours eventually progress to an anti-androgen-resistant state and there remains a large unmet

Figure 1 (A) Identification of direct androgen receptor (AR) target genes by combining three sets of genome-wide data: The identification of AR DNA-binding regions; the identification of regions that recruit RNA polymerase II; and androgen-induced effects on global gene expression profiles. (B) Cellular processes regulated by direct AR target genes. Expression of the direct AR target CAMKK2 correlates with prostate cancer development, and its upregulation leads to changes in metabolic fluxes in the cell.

medical need for prostate cancer treatments. AR functions as a ligand-activated transcription factor that binds to DNA to control target gene expression. Since the initial cloning of AR (Lubahn *et al*, 1988), molecular mechanisms associated with androgen signalling have begun to be revealed, with an improved understanding of ligand–receptor interactions, receptor–DNA interactions and receptor–cofactor interactions (Bennett *et al*, 2010). This knowledge has facilitated the development of prostate cancer therapies targeted more broadly at AR signalling (Chen *et al*, 2008). However, until now there has been a lack of systematic investigations of androgen signalling in cancer development, particularly in terms of the interplay between AR-controlled transcriptional regulatory networks and other important cellular processes such as metabolism.

Using two prostate cancer cell lines as model systems, Massie *et al* identified a set of direct AR target genes by a strategy combining three sets of genome-wide data and introducing various filters during the data analysis process. The identification of these direct AR target genes constitutes a critical part of the study. By combining global AR DNA-binding regions with RNA polymerase II recruitment regions, they delineate a set of what they term core AR-binding regions. Further combining this data set, restricted to within 25 kb of a gene, with a time course of global expression profiles of androgen-regulated genes, they define what they refer to as the direct AR target genes (Figure 1A).

Interestingly, subsequent bioinformatics analysis revealed a significant enrichment of metabolic regulatory genes among the direct AR target genes. Many key players in glucose uptake, glycolysis and anabolism were identified as direct AR target genes. Importantly, a comprehensive metabolomics profiling assessing the effects of AR signalling on glucose consumptions, lactate production, and intracellular and extracellular metabolites confirmed the role of AR signalling in stimulating aerobic glycolysis and anabolism in prostate cancer cells (Figure 1B). These findings demonstrate an

important connection between metabolism and cancer growth control, highlighting important avenues for future target discovery.

In a next step, Massie *et al* used meta-analysis of global gene expression profiles from clinical samples to refine the set of the direct AR target genes obtained from cell line models. CAMKK2 was highlighted as a direct target whose expression was consistently upregulated in prostate cancer. CAMMK2 has previously been shown to contribute to the regulation of energy homeostasis by regulating a metabolic master molecule, AMPK, in the hypothalamus (Anderson *et al*, 2008). The role of CAMKK2 as a metabolic master regulator mediating AR actions in this context was established by a series of studies in cell lines and animal models, confirming the critical role of CAMKK2 in cellular metabolism and prostate cancer growth (Figure 1B). Of particular importance is the observation that CAMKK2 holds promise as a drug target in both androgen-dependent and androgen-resistant prostate cancer.

Driven by technological advances, high-throughput technologies and bioinformatics have changed the ways in which research is performed, and an increasingly integrative approach to biology seems inevitable, as it offers an important complement to a more reductionist approach and a route forward (Macilwain, 2011). The union of biology and mathematics has provided Massie *et al* with the tools to identify CAMKK2 as a potential drug target that holds promise for development of novel therapies for a disease where there remains a large unmet medical need. Still, identification of drug targets is just the beginning of a long journey; bringing that knowledge into clinical practice presents an extreme challenge. Hopefully, this study will be followed by additional novel approaches to increase the chances that a compound is finally brought through the hurdles of drug discovery to bring a drug to the market for the benefit of patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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