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Prostate Cancer Regulatory Networks

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Abstract

Although the timing with which common epithelial malignancies arise and become established remains a matter of debate, it is clear that by the time they are detected these tumors harbor hundreds of deregulated, aberrantly expressed or mutated genes. This enormous complexity poses formidable challenges to identify gene pathways that are drivers of tumorigenesis, potentially suitable for therapeutic intervention. An alternative approach is to consider cancer pathways as interconnected networks, and search for potential nodal proteins capable of connecting multiple signaling networks of tumor maintenance. We have modeled this approach in advanced prostate cancer, a condition with current limited therapeutic options. We propose that the integration of three signaling networks, including chaperone-mediated mitochondrial homeostasis, integrin-dependent cell signaling, and Runx2-regulated gene expression in the metastatic bone microenvironment plays a critical role in prostate cancer maintenance, and offers novel options for molecular therapy.

Keywords

PROSTATE CANCER; SIGNALING; REGULATORY NETWORKS; RUNX; SURVIVIN; INTEGRINS

CANCER PATHWAYS AND CANCER NETWORKS IN TARGETED THERAPY

Cancer treatment now aims at disabling signaling mechanisms essential for tumor maintenance without affecting normal tissues, that is, targeted therapy [Sawyers, 2004; Strausberg et al., 2004]. This is urgently needed because mainstay anticancer agents, such as cytotoxics [Chabner and Roberts, 2005], and radiation [Bernier et al., 2004], have reached a plateau in the

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management of many cancers, and their efficacy is invariably reduced by side effects, and drug resistance [Stein et al., 2004]. As pioneered by the BCR-ABL kinase inhibitor, Imatinib mesylate [O'Dwyer and Druker, 2000], targeted cancer therapy is feasible and can produce spectacular clinical responses [Deininger et al., 2005]. In addition, tumors can become "addicted" to a primary oncogenic lesion [Weinstein and Joe, 2006], and targeted therapy of these pathways may generate impressive responses, at least in certain patients [Sharma et al., 2007]. Finally, the recent availability of genome-wide profiling of tumors [Perou et al., 2000; van de Vijver et al., 2002], may help tailor targeted intervention for likely responders, and realize the concept of "personalized cancer therapy" [Drews, 2006].

Despite these gains [Sawyers, 2004], the enormous genetic heterogeneity of seemingly identical tumors [Vogelstein and Kinzler, 2004], with hundreds of mutated, amplified or deregulated genes [Sjoblom et al., 2006; Wood et al., 2007], makes it difficult to identify in most cases a single, "driving" signaling pathway suitable for therapeutic intervention. For this reason, traditional, "target-centric' drug discovery pursuing the development of "Imatinib-like" agents [Guillemard and Saragovi, 2004], has produced less than optimal results [Butcher, 2005]. Costly, labor intensive, and low yield (~1 in a million high throughput hits makes it to the clinic) [van der Greef and McBurney, 2005], this approach has generated many hopeful drugs, which all too often produced modest, or no gains in cancer patients [Schein and Scheffler, 2006].

As an alternative, efforts have begun to exploit systems biology tools [Araujo and Liotta, 2006] to model cancer pathways in their globality, rather than focusing on individual genes [Rajasethupathy et al., 2005]. Connectivity maps [Lamb et al., 2006] linking together multiple signaling mechanisms of tumor maintenance [Lamb, 2007], may more faithfully recapitulate the "tumor tactics" [Kitano, 2003] responsible for treatment failure, including pathway redundancy, buffering, and modularity into semi-autonomous sub-networks [Butcher, 2005; Rajasethupathy et al., 2005]. From a therapeutic standpoint, analysis of cancer networks may identify "nodal" or "hub" proteins [van der Greef and McBurney, 2005], molecules that integrate multiple sub-networks, with *essential* roles in tumor maintenance [Butcher, 2005; Rajasethupathy et al., 2005]. An example of a cancer nodal protein is the EGF receptor [Citri and Yarden, 2006], which connects extracellular cues to panoply of downstream intracellular responses [Sharma et al., 2007]. For their properties, nodal proteins are prime targets for a novel "pathway-oriented" drug discovery. In this context, antagonists of these molecules may function as global *pathway inhibitors* [Butcher, 2005; van der Greef and McBurney, 2005], simultaneously disabling multiple signaling networks regardless of tumor heterogeneity.

CHALLENGES OF ADVANCED PROSTATE CANCER

Although significant gains have been made in the management of the early phases of prostate cancer, when expansion and maintenance of the transformed cell population is largely fueled by hormone-dependency, the evolution of prostate cancer to a hormone-independent stage invariably signals advanced disease, with limited therapeutic options and poor prognosis. Although such progression requires decades to become clinically relevant [Draisma et al., 2003], and only in certain cases [Carter, 2006], the acquisition of independence from chemical or surgical castration is often fatal within 24 months [Berthold et al., 2008]. At a molecular level, this involves a poorly understood cascade of events, but clearly reflecting enormous molecular, cellular and genetic heterogeneity, including amplification of the *androgen receptor* locus with hypersensitivity at low hormone concentrations [Chen et al., 2004], promiscuous receptor activation by non hormone-regulated molecules, including growth factor receptors [Culig et al., 1994], or cytokines [Wallner et al., 2006], and clonal selection of androgen-independent tumor cells [Collins et al., 2005]. Advanced prostate cancer is also associated with metastatic dissemination, typically to the bones, causing both osteoblastic and

osteolytic lesions [Loberg et al., 2005]. The therapeutic options for these patients are limited, and only docetaxel-based chemotherapy, together with biphosphonate palliation of bone lesions, has been shown to modestly prolong survival.

With the realization of the extreme complexity of advanced prostate cancer, several new therapeutic strategies are being envisioned to disable multiple networks of tumor maintenance, rather than an individual signaling pathway. These include growth factor receptor signaling, angiogenesis, the "tumor microenvironment," various anti-apoptotic mechanisms, integrin-mediated cell adhesion, as well as enhancing antitumoral immunity [reviewed in Taichman et al., 2007]. Hsp90 inhibition is also being considered in this setting, with the hope of disabling signaling kinases and non-hormone regulated androgen receptor activation [Taichman et al., 2007]. Although promising, it is too soon to tell whether any of these "pathway-oriented" approaches will have a meaningful impact in the clinic. At the present time, advanced and metastatic prostate cancer remains a deadly disease, with only palliative therapeutic options, and an area in urgent need of new molecular and translational research advances. In this context, recent collaborative work has identified three interconnected signaling networks of pivotal significance in the pathogenesis and progression of advanced prostate cancer. These include a novel pathway of mitochondrial homeostasis regulated by Hsp90 molecular chaperones, a pleiotropic signaling cascade initiated by the integrins at the cell surface, and a transcriptional network orchestrated in the bone microenvironment by Runx2. Each of these interconnected networks is regulated by unique nodal proteins, which provide unique therapeutic opportunities for "pathway-oriented" drug discovery.

THE FIRST PROSTATE CANCER REGULATORY SUBNETWORK: HSP90 CHAPERONE CONTROL OF MITOCHONDRIAL HOMEOSTASIS

Mitochondrial dysfunction plays a pivotal role in the initiation of apoptosis, or programmed cell death [Green and Kroemer, 2004]. Triggered by disparate stimuli, this process involves a complex molecular cascade [Ferri and Kroemer, 2001], characterized by increased permeability of the mitochondrial inner membrane, loss of membrane potential, swelling of the matrix, and rupture of the outer membrane [Kroemer and Reed, 2000; Green and Kroemer, 2004]. In turn, damaged mitochondria release apoptogenic proteins, in particular cytochrome *c* in the cytosol [Zamzami and Kroemer, 2001], which mediates activation of initiator and effector caspases [Hengartner, 2000]. How this "mitochondrial permeability transition" is regulated in not completely understood, but what it is clear is that mechanisms to antagonize its execution are often exploited or subverted in tumor cells. Pro-apoptotic Bcl-2 molecules [Cory and Adams, 2002], including multi-domain Bax and Bak [Wei et al., 2001], or so-called "BH3-only" members, contribute to permeabilize the outer membrane, with release of cytochrome *c* [Green and Kroemer, 2004]. Conversely, the molecular organization of a mitochondrial permeability transition "pore" [Crompton et al., 1999], which mediates swelling of the matrix and depolarization of the inner membrane, has remained elusive. Based on knockout studies in mice, two long-held constituents of this pore, the voltage-dependent anion channel (VDAC) [Baines et al., 2007], and the adenine nucleotide translocator (ANT) [Kokoszka et al., 2004], turned out to be dispensable for cell death. Instead, knockout data showed that the matrix peptidyl prolyl-*cis, trans* isomerase immunophilin, Cyclophilin D (CypD) [Woodfield et al., 1998], was indispensable for mitochondrial permeability transition, especially in response to oxidative stress or Ca^{2+} overload [Baines et al., 2005; Nakagawa et al., 2005; Schinzel et al., 2005].

How CypD function is regulated is not completely clear, but this process may involve protein folding mechanisms. Accordingly, it has been proposed that assembly of a permeability transition pore may be a dynamic process, in which mitochondrial damage, such as Ca^{2+} overload or reactive oxygen species, generates clusters of unfolded proteins that ultimately

promote opening of a CypD-containing pore [He and Lemasters, 2002]. This model predicts that protein refolding mechanisms in mitochondria (see below) may be ideally suited to counterbalance permeability transition, prevent CypD-mediated pore opening, and preserve organelle integrity [He and Lemasters, 2003]. Other regulators of mitochondrial cytoprotection have also been described, including a pool of the Inhibitor of Apoptosis (IAP) protein [Eckelman et al., 2006], survivin [Altieri, 2008]. Mitochondrial survivin may oppose the release of apoptogenic proteins, cooperatively inhibit caspase activation in the cytosol [Dohi et al., 2004, 2007], or intrinsically regulate the permeability transition pore in mitochondria. Despite these gaps in our understanding of mitochondrial homeostasis, efforts to manipulate these pathways and trigger apoptosis in cancer cells [Fesik, 2005; Oltersdorf et al., 2005], have recently reached the clinic [Johnstone et al., 2002]. However, it is unclear whether these approaches can selectively discriminate between normal and transformed cells [Verma et al., 2003; Foster et al., 2006], or whether the extreme redundancy of Bcl-2 proteins as regulators of outer mitochondrial integrity may ultimately result in emergence of drug resistance [Konopleva et al., 2006; Deng et al., 2007].

Recent studies identified an abundant pool of Hsp90, and its related chaperone, TRAP-1 [Felts et al., 2000], in mitochondria of tumor, but not most normal tissues, in vivo [Kang et al., 2007]. Expression of TRAP-1 is particularly abundant in advanced prostate cancer with high Gleason scores, and prostate cancer metastasis to bones and lymph nodes, but undetectable in normal prostate, or prostatic intraepithelial neoplasia, in vivo. Although the basis for this "tumor-specific" localization is unclear, mitochondrial Hsp90 chaperones function as novel CypD-associated molecules, in a recognition that requires the isomerase activity of CypD [Kang et al., 2007]. In turn, this interaction antagonizes CypD-mediated pore-forming function, prevents permeability transition, and suppresses the initiation of apoptosis [Kang et al., 2007]. Cytoprotection by mitochondrial Hsp90 requires the chaperone protein folding activity [He and Lemasters, 2002], and is *essential* to maintain organelle integrity. Accordingly, a peptidomimetic Hsp90 inhibitor [Meli et al., 2006], Shepherdin [Plescia et al., 2005], capable to accumulate in mitochondria induced collapse of organelle homeostasis, with loss of membrane potential, release of cytochrome *c*, and massive apoptosis [Kang et al., 2007]. In contrast, normal cell types that do not have Hsp90 in mitochondria were not affected [Kang et al., 2007], including $CD34^+$ hematopoietic progenitor cells [Plescia et al., 2005; Gyurkocza et al., 2006]. Recent studies independently confirmed a general cytoprotective function of mitochondrial Hsp90 chaperones, including TRAP-1, and established their role in inhibition of cytochrome *c* release [Masuda et al., 2004], and suppression of apoptosis [Hua et al., 2007], especially in response to oxidative stress [Pridgeon et al., 2007].

THE SECOND PROSTATE CANCER REGULATORY SUBNETWORK: SIGNALING BY α_V INTEGRINS

Integrins comprise a family of cell surface receptors composed of non-covalently bound α and β subunits, which can combine in at least 24 different complexes [Alam et al., 2007]. These molecules mediate attachment of cells to the extracellular matrix (ECM) and have also been implicated in activation of disparate signaling pathways [Hynes, 2002; Alam et al., 2007]. In cancer, integrin signaling is exploited to affect cellular growth and tumor progression by controlling apoptosis, cell adhesion, proliferation, gene expression, and migration [Felding-Habermann, 2003; Akalu et al., 2005]. In addition, integrin signaling has been shown to act as a mechanism to regulate proteinase expression [Munshi and Stack, 2006]. These mechanisms are particularly relevant in prostate cancer, where tumor cells have a different surrounding matrix compared to normal cells, so that changes in integrin profile may functionally contribute to the growth and establishment of primary and metastatic foci [Fornaro et al., 2001; Demetriou and Cress, 2004; Goel et al., 2008]. Several studies have associated deregulated integrin expression with the progression of prostate cancer to an advanced stage [Knox et al., 1994;

Murant et al., 1997; Goel et al., 2008]. In this context, most α and β subunits have been shown to be downregulated in prostate cancer, whereas predominantly α_6 and α_V integrins are upregulated [Goel et al., 2008], suggesting a potential role for these receptors in the progression of this disease toward an androgen-independent castration-resistant metastatic state. Although the molecular pathways by which integrins contribute to cancer progression and metastasis need to be fully elucidated, designing new therapeutic approaches for prostate cancer based on inhibiting integrin functions, integrin cleavage or integrin downstream signaling is likely to be a successful strategy.

Many efforts have been made, to inhibit prostate cancer metastasis to bone, the most common metastatic site for this disease; however, the current therapies are not very efficacious. Since integrins mediate the interactions between tumor cells and the bone microenvironment, a potential application of the use of integrin inhibitors is to prevent prostate cancer growth in bone [Waltregny et al., 2000; Pecheur et al., 2002; Karadag et al., 2004; Hall et al., 2006; King et al., 2008]. A recent study has shown that the $\alpha_v\beta3$ integrin promotes bone gain mediated by metastatic prostate cancer cells and suggest that $\alpha_v\beta3$ is a potential therapeutic target to block prostate cancer osteoblastic lesions [Keller and Brown, 2004; McCabe et al., 2007]. In this context, evidence has been provided supporting a role for α_v integrins in prostate cancer cell survival in bone [Bisanz et al., 2005].

In conclusion, these promising investigations indicate that the clinical use of integrins' inhibitors spans all stages of cancer progression from inhibition of tumor growth to inhibition of metastasis.

THE THIRD PROSTATE CANCER REGULATORY SUBNETWORK: RUNX2 CONTROL OF GENE EXPRESSION IN THE BONE METASTATIC MICROENVIRONMENT

As indicated above, one the most common and, unfortunately, most severe developments in prostate cancer progression is the emergence of metastatic lesions to the bone [Cereceda et al., 2003]. Patients with bone metastases have severe bone pain, spinal cord compression, and osteolysis, which compromises structural integrity of bone with increased susceptibility to fractures [Roodman, 2004]. Prostate cancers that metastasize to bone secrete factors (e.g., endothelin-1, BMP2) that result primarily in osteoblastic lesions, as well as osteolytic bone disease [Keller and Brown, 2004; Roudier et al., 2008] induced by secreted PTHrP and TGFβ [Bendre et al., 2003; Kingsley et al., 2007; Pratap et al., 2008]. It is now appreciated from animal models that osteolysis occurs prior to the osteoblastic lesions in prostate cancer metastatic bone disease.

Considerable effort has been devoted to map the requirements of bone lesions in prostate tumors. Experimental evidence suggests that osteoblast lesions originate from the recruitment of bone-forming cells into the tumor environment [Li et al., 2008b], and this process is also contributed by the expression of transcription factors by prostate cancer cells activating bank of genes with osteomimetic properties, potentially contributing to formation of woven bone within the tumor [Guise et al., 2006]. Thus, the metastasis of prostate cells to bone is a continuum of degeneration of the skeleton with ectopic bone formation in the tumor, often associated with resistance to conventional therapy [FitzGerald et al., 2008]. In the past few years, bioinformatics approaches combined with micro-array gene profiling of primary tumors and cell lines have provided important data for identification of gene signatures of disease progression [Dairkee et al., 2004; Smid et al., 2006]. In this context, recent data have demonstrated that Runx2, a transcription factor essential for osteogenesis, becomes highly

activated in prostate cancer cells that metastasize to bone, and is detected in human and mouse prostate cancer tissue, but not normal prostate, in vivo [Yang et al., 2004].

Recent studies have expanded this view, and identified Runx2 as a key regulator of bone metastasis [Pratap et al., 2006]. When abnormally expressed in tumor cells, Runx2 has pathological functions that are deregulated compared to normal cells: Runx2 is no longer antiproliferative, and instead appears to have oncogenic properties, as demonstrated by synergism with c-Myc [Vaillant et al., 1999; Blyth et al., 2001], and in promoting aggressive tumor growth in the bone [Barnes et al., 2004]. At a molecular level, Runx2-mediated tumor progression and metastasis involves regulated interactions with co-regulatory molecules, including chromatin remodeling factors, intracellular mediators of signaling pathways and other transcription factors [Lian et al., 2004; Pratap et al., 2006]. In prostate cancer [Brubaker et al., 2004], Runx2 has been associated with the osteomimetic properties of bone metastatic cells [Zayzafoon et al., 2004; Pratap et al., 2006], via transcription of genes implicated in osteoblastic lesions [Zhang et al., 2003; Brubaker et al., 2004; Dai et al., 2004]. These include ECM proteins (osteocalcin, bone sialoprotein, and osteopontin), signaling molecules (vascular endothelial growth factor), and enzymes involved in bone turnover (matrix metalloproteinases) [Yang et al., 2001; Pratap et al., 2006]. In contrast, non-metastatic cells exhibit low levels of Runx2 [Brubaker et al., 2003; Inman and Shore, 2003; Barnes et al., 2004; Selvamurugan et al., 2004; Javed et al., 2005; Pratap et al., 2005].

A UNIFIED AND INTEGRATED PROSTATE CANCER REGULATORY NETWORK: IMPLICATIONS FOR DISEASE PROGRESSION AND PATHWAY-ORIENTED DRUG DISCOVERY

Recent experimental evidence suggests that the three regulatory networks outlined above are extensively interconnected, sharing common signaling pathways, and utilizing a common set of effector and nodal molecules. In addition, because of their synergistic role in fundamental mechanisms of disease progression and metastatic dissemination, these pathways and their associated nodal proteins may provide novel opportunities for pathway-oriented drug discovery. Specifically, analysis of subnetwork interactions using systems biology tools reveals an extensive degree of connectivity (Fig. 1). The first Hsp90 subnetwork interfaces extensively with Runx2 regulation of gene transcription in the bone microenvironment, controls multiple pathways of cell survival often exploited in prostate cancer, and regulates the stability and function of multiple effector molecules of integrin signaling (Fig. 1). The second subnetwork of α_V integrin-initiated signal transduction also interfaces with critical components of mitochondrial cell death, preserving cell viability, controlling Runx2 transcriptional activity through modifications in Runx2 phosphorylation [Sun et al., 2001;Chang et al., 2008], and integrates matrix metalloproteinase and TGFβ signals of pivotal importance for metastatic dissemination, especially to the bones (Fig. 1). This is mirrored by a comparable set of interactions involving the third subnetwork of Runx2-dependent gene expression, which affects integrin expression and signaling, mitochondrial integrity via Bax regulation of outer membrane permeability, and modulation of TGFβ responses in both early and late events of prostate cancer tumorigenesis, and metastatic bone disease [Mundy, 2002;Buijs et al., 2007;Nguyen and Massague, 2007;Baselga et al., 2008;Pratap et al., 2008;Li et al., 2008a] (Fig. 1). In addition, this integrated regulatory network utilizes common nodal proteins. Survivin is a regulator of apoptosis participating in prostate cancer progression [Altieri, 2008] that is implicated in mitochondrial homeostasis, and whose expression in prostate cancer is controlled by both Runx2- and integrin-initiated signaling. Similarly, Hsp90 homeostasis has also been implicated in preservation of mitochondrial integrity [Kang et al., 2007], but also in the control of pivotal client proteins [Whitesell and Lindquist, 2005] of the second and third

subnetworks, including TGFβ, and androgen receptor (AR), as well as in the direct contribution of cell invasion and metastasis [Eustace et al., 2004].

In this context, it may be possible to envision the development and characterization of a novel set of "network inhibitors" capable of targeting the nodal proteins in this integrated set of pathways. Although small molecule antagonists of Hsp90 have now reached the clinic, their therapeutic efficacy as single agents has been modest, at best, generally below the expectations for these agents to function as genuine pathway antagonists. The regulatory network outlined above suggests that the segregation of Hsp90 in specialized subcellular compartments, including mitochondria, may provide novel options for the development of targeted inhibitors. In this context, proof-of-principle experiments to target Hsp90 inhibitors to mitochondria have produced encouraging results, causing mitochondrial collapse in tumor cells, accompanied by sudden and massive cell death and inhibition of tumor growth in preclinical experiments, in vivo. Similar considerations apply to the potential role of integrins as cell surface receptors, drugable targets. In this context, the α_V integrins are emerging as an attractive molecular target for inhibition of an integrated network of cell invasion and migration, including pleiotropic TGFβ signaling responses. This may be particularly relevant in prostate cancer, where interference with metastatic bone colonization frequently involves deregulation of TGFβ functions. Lastly, although transcription factors are typically considered non-drugable, therapeutic targeting of Runx2 by local delivery of short hairpin RNA (shRNA) could interrupt an integrated network of gene expression required to maintain the metastatic niche in the bone microenvironment, and concomitantly deregulate cell survival and cell migration pathways of invading prostate cancer cells.

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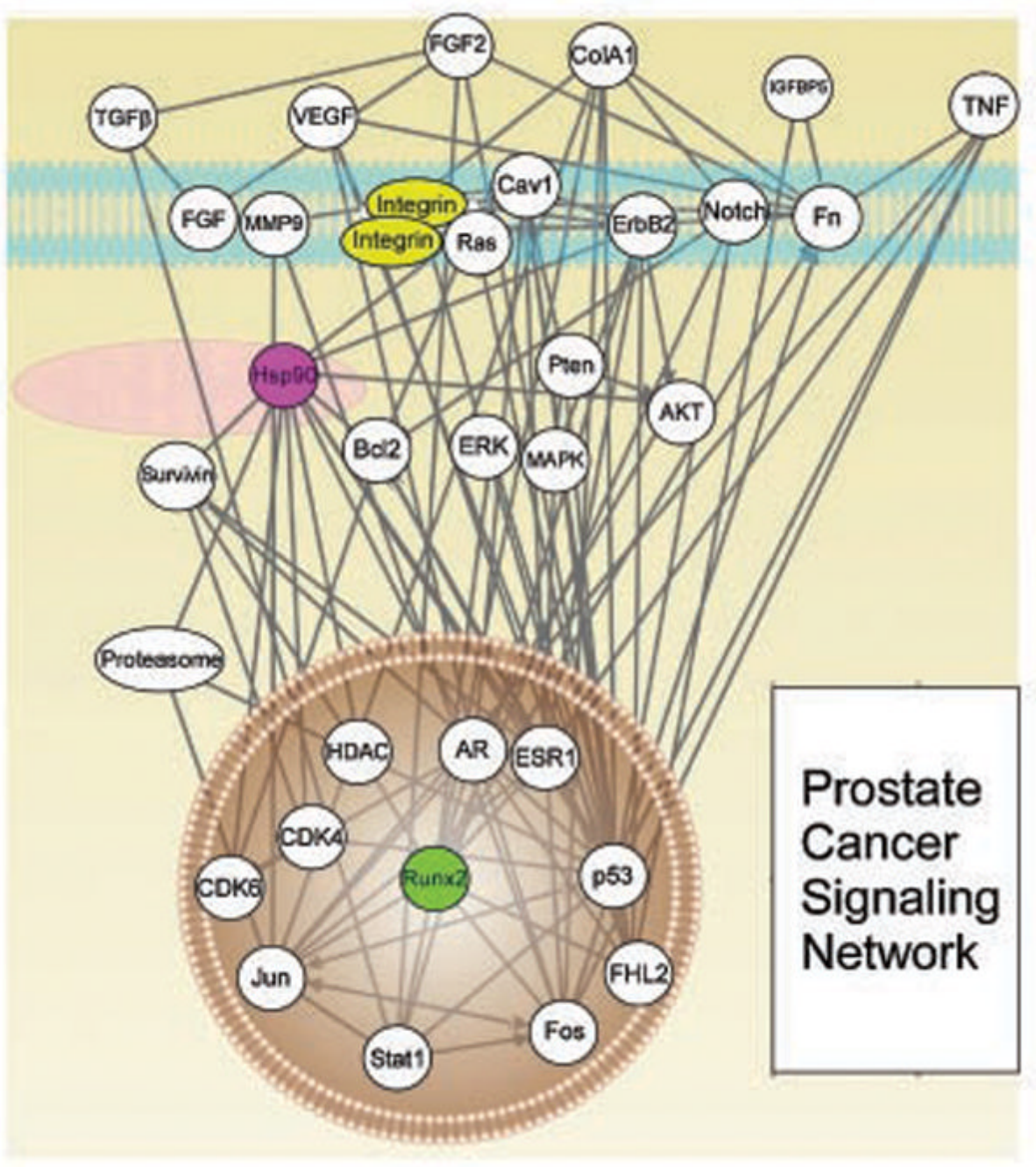

Fig. 1.

Prostate Cancer Signaling Network. The integration of regulatory pathways in plasma membrane (integrins), cytosol (Hsp90), and nucleus (Runx2) that provide therapeutic targets in prostate cancer is indicated.