

# Role of $\alpha V\beta 3$ in Prostate Cancer: Metastasis Initiator and Important Therapeutic Target

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**Abstract:** In prostate cancer, distant organ metastasis is the leading cause of patient death. Although the mechanism of malignant tumor metastasis is unclear, studies have confirmed that integrin  $\alpha V\beta 3$  plays an important role in this process. In prostate cancer,  $\alpha V\beta 3$  mediates adhesion, invasion, immune escape and neovascularization through interactions with different ligands. Among these ligands and in addition to proteins that are directly related to tumor invasion, other proteins that contain the RGD structure could also bind to  $\alpha V\beta 3$  and cause a number of biological effects. In this article, we summarized the ligand and downstream proteins related to  $\alpha V\beta 3$ -mediated prostate cancer metastasis as well as some diagnostic and therapeutic measures targeting  $\alpha V\beta 3$ .

**Keywords:** prostate cancer, metastasis,  $\alpha V\beta 3$ , signal pathway

## Introduction

According to Cancer Statistics, 2020, the incidence of prostate cancer (PCa) is as high as 21%, ranking first among tumor diseases and second among expected causes of cancer-related death in American male patients.<sup>1</sup> In the early stage of PCa, androgen is the main factor that regulates tumor growth.<sup>2,3</sup> In the clinic, androgen deprivation therapy is used to treat PCa and has achieved ideal therapeutic effects.<sup>2</sup> However, after a period of treatment, tumor cells are transformed from androgen-dependent into androgen-independent cells and become insensitive to chemotherapy.<sup>4</sup> Recrudescence tumor growth is often faster and associated with an increased metastasizing tendency.<sup>5,6</sup> Bone is the most common metastasizing site of PCa.<sup>7</sup> Patients often suffer from bone pain and pathological fractures, which not only seriously affect the quality of life but also directly lead to patient death.<sup>8</sup> Therefore, studying the mechanism of PCa metastasis is important to prevent PCa bone metastasis and prolong patient survival.

Metastasis is a process that involves interactions between the cell and extracellular matrix (ECM) as well as cell and target organ.<sup>9–11</sup> At the beginning of metastasis, tumor cells must destroy the ECM as this structure prevents cancer cells from leaving their primary site. Cells must survive in the vasculature and finally be deposited in the corresponding tissue.<sup>12,13</sup> Currently, a large number of in vivo and in vitro studies have found that the integrin protein family is involved in the entire process of tumor cell invasion and metastasis.<sup>5,7,10,14</sup> In PCa,  $\alpha V\beta 3$  is the most studied integrin during metastasis. Integrin  $\alpha V\beta 3$  regulates tumor cell adhesion and migration by combining with extracellular matrix ligands and cell-surface ligands.<sup>10,15</sup> Dissociative ligand, which contains the RGD structure (Arg-Gly-

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Asp), is recognized by integrin and triggers signaling to modulate the biological behavior of cells. The structure of  $\alpha V\beta 3$  contains transmembrane  $\alpha\beta$  heterodimers, and analyses of the crystal structures of integrin  $\alpha V\beta 3$  revealed a ligand-binding site on the headpiece of the  $\alpha V\beta 3$  region. This region is composed of the  $\alpha$  and  $\beta$  subunits, ie, the  $\beta$ -propeller domain and the plexin-semaphorin-integrin (PSI) domain of the  $\alpha V$  subunit and the  $\beta I$ -like domain and the hybrid domain of the  $\beta$  subunit. In particular, the ligand that contains an RGD sequence is directly recognized by amino acid residues at the interface between the  $\beta$ -propeller domain and the  $\beta I$ -like domain.<sup>15</sup>

It has been reported that  $\alpha V\beta 3$  is necessary for tumor cell adhesion to the ECM by targeting the RGD in fibronectin. Once cells adhere on to the ECM, the signal is transmitted intercellularly through the  $\beta$ -subunit. Inside the cell membrane, focal adhesion kinase (FAK), Paxillin and Zyxin gather at the tail of the  $\beta$ -subunit to form a trimer, which connects with the cytoskeleton (such as actin) to promote cytoskeletal protein rearrangement (to eventually yield protein fiber contraction). This series of changes eventually led to cell shape changes via transmission to the next  $\alpha V\beta 3$  molecule.<sup>16,17</sup>

Integrin  $\alpha V\beta 3$  not only directly interacts with ECM but also regulates MMP (especially MMP-2 and MMP-9) expression through the PI3K signaling pathway to hydrolyze collagen in the ECM.<sup>18–20</sup> When tumor cells permeate into microvascular or lymphatic vessels,  $\alpha V\beta 3$  recruits some proteins with affinity to protect cells from complement or immune cell attack.<sup>21,22</sup> When tumor cells successfully reach the target organ,  $\alpha V\beta 3$  acts as a receptor for VEGF to promote neovascularization, providing blood supply to the tumor cell mass and aiding in the establishment of metastases.<sup>23</sup>

These above functions of  $\alpha V\beta 3$  are not ascribed to its own activities but rather a series of extracellular ligands and intracellular signaling pathways that participate in the overall effect. Therefore, in this article, we have summarized the ligands and the downstream proteins related to  $\alpha V\beta 3$  regulating PCa metastasis to help researchers better understand the mechanism by which  $\alpha V\beta 3$  regulates tumor metastasis.

## Extracellular or Membrane Ligands Combine with/Activate $\alpha V\beta 3$

Although  $\alpha V\beta 3$  plays a dominate role in the progress of malignant metastasis, some extracellular or membranous

ligands are indispensable for actuate invasion through the regulation of  $\alpha V\beta 3$  activation. As previously mentioned, the RGD sequence is specifically recognized by the  $\alpha V\beta 3$  binding site; thus, the majority of the ligand contains an RDG structure. SIBLING family proteins, such as bone sialoprotein (BSP) and osteopontin (OPN) are the classical ligand of  $\alpha V\beta 3$  (Figure 1).<sup>24</sup> These proteins bind to  $\alpha V\beta 3$  with the help of RGD to hydrolyze ECM. However, the RGD sequence is not an absolute factor for ligand recognition by  $\alpha V\beta 3$ . Several recent studies have demonstrated that cell chemokines and membrane ion channels, such as CXCL16 and BKCa, respectively, are also involved in  $\alpha V\beta 3$ -mediated metastasis. We will summarize the activation of  $\alpha V\beta 3$  by different ligands below.

## The SIBLING Family Regulates PCa Metastasis in an $\alpha V\beta 3$ -Dependent Manner

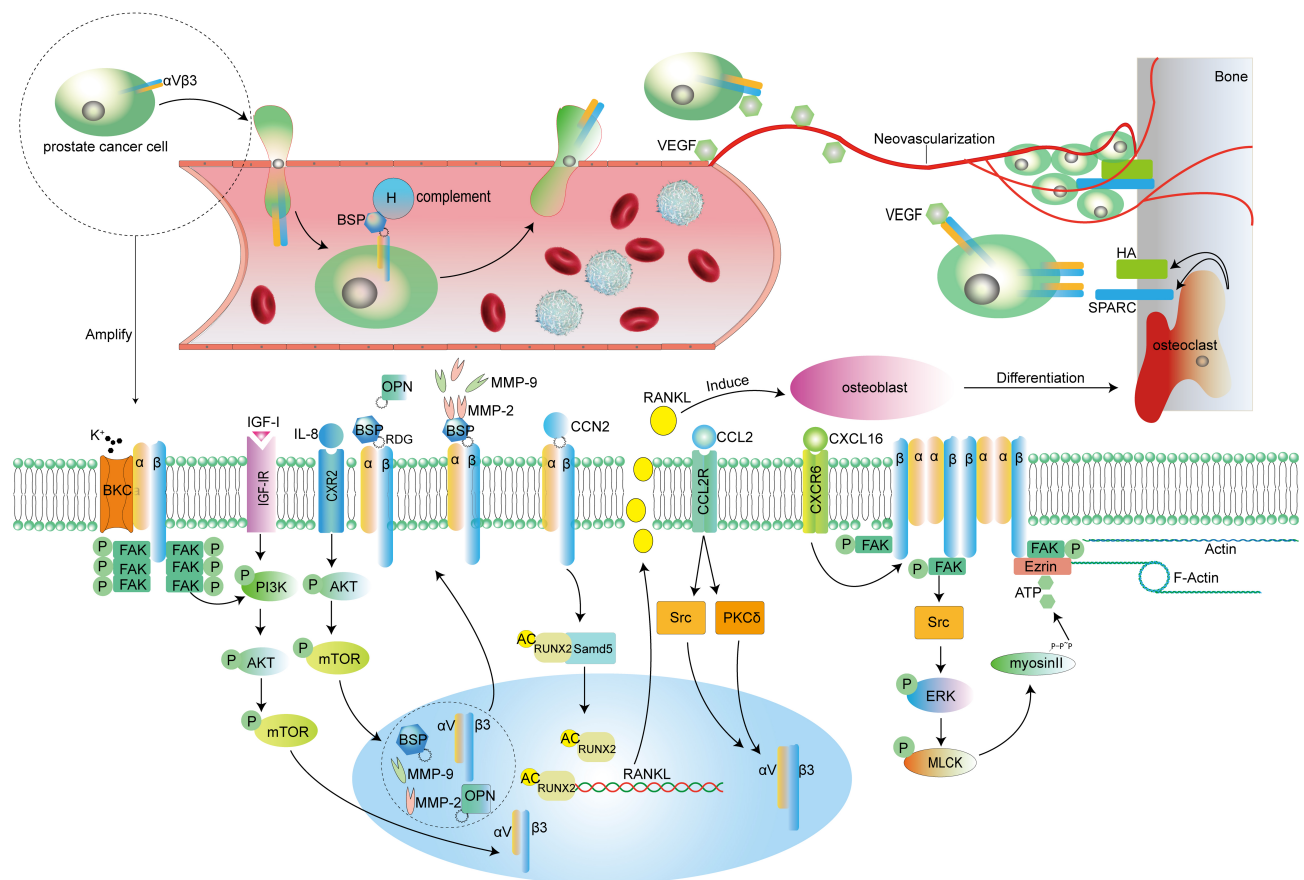
Small integrin-binding ligand N-linked glycoproteins (SIBLINGS) are soluble glycoprophosphoproteins, and members of the SIBLING family include osteopontin (OPN), bone sialoprotein (BSP), dentin matrix protein 1 (DMP1), dentin sialo-phosphoprotein (DSPP) and matrix extracellular phosphoprotein (MEPE). BSP and OPN have been more extensively studied than other SIBLING proteins.<sup>24–29</sup> These two proteins have been identified as primary inducers in the progression of PCa metastasis, especially bone metastasis. As mentioned previously, BSP and OPN contain an integrin-binding RGD sequence, which can bind to  $\alpha V\beta 3$  on the cell surface. After these proteins are immobilized on the tumor cell membrane with the help of  $\alpha V\beta 3$ , BSP or OPN recruit matrix metalloproteinases (for example: MMP-2 and MMP-9) to hydrolyze ECM and promote tumor cell dissemination and seeding in other organs.<sup>15,24,30,31</sup> When tumor cells invaded into the vasculature,  $\alpha V\beta 3$  bound to BSP binds to complement factor H to protect tumor cells from complement attack. After prostate cancer cells pass the blood vessel endothelium and reach the target organ, particularly bone, blood supply becomes the most important factor for tumor survival. Aditi Gupta et al demonstrated that OPN and VEGF act as important regulators of angiogenesis via the integrin  $\alpha V\beta 3$  signaling pathway involved in cancer cell growth.<sup>32–34</sup> These researchers found that OPN induces angiogenesis by enhancing the expression of VEGF in PC3 cells. In this process, integrin is the main intermediary because the mutated RGD sequence of OPN leads to decreased VEGF expression. After treating PC3 with an  $\alpha V\beta 3$  antagonist,

VEGF cannot be restored to its original level even if OPN is overexpressed in PC3.

## Connective Tissue Growth Factor Utilizes $\alpha V\beta 3$ as a Receptor to Mediate PCa Bone Metastasis

Connective tissue growth factor (CTGF), which is also referred to as CCN2, is a small secreted matrix protein that regulates various cellular functions, including proliferation, adhesion, migration, and invasion.<sup>35–38</sup> Under physiological conditions, CCN2 induces skeletogenesis, angiogenesis, and injury repair.<sup>39</sup> However, pathologically,

CCN2 is closely related to cancer bone metastasis.<sup>40,41</sup> It has been reported that  $\alpha V\beta 3$  act as a major receptor for CCN2 and mediates the migration and adhesion of endothelial and hepatic stellate cells (Figure 1). Based on this theory, Bongjun Kim et al assessed the relationship between CCN2 and  $\alpha V\beta 3$  in PCa. They found that CCN2 increases matrix invasion activity of the bone metastatic cell line PC3 by upregulation of RUNX2 levels by modulating the promoter activity of RUNX2, which induces the expression of MMP-2 and MMP-9 proteins. These effects were abolished when PC3 cells were treated with an anti- $\alpha V\beta 3$  antibody. To promote growth outside of the primary organ, cancer cells must transform the tissue



**Figure 1** The figure describes the process by which  $\alpha V\beta 3$  mediates prostate cancer cell metastasis. Macroscopically, after cancer cells destroy the ECM and leave their primary site, cancer cells depend on  $\alpha V\beta 3$ , which destroys vascular endothelial cells, to enter blood vessels. In blood vessels, tumor cells under the protection of BSP escape the attack of the immune system and then pass through the blood vessels to reach the metastatic site. Here, bone tissue is used as an example. Under the induction of VEGF, cancer cells recognize SPARC and HA and interact with them on the surface of bone with the help of  $\alpha V\beta 3$ ; at the same time, VEGF induces neovascularization to supply blood to the cell mass system. At the microscopic level, IL-8, IGF-1, CCN2 and other ligands activate different signaling pathways to promote the expression of  $\alpha V\beta 3$  in cancer cells. In addition, CCN2 transmits signals into the cell through  $\alpha V\beta 3$  to increase the acetylation of the transcription factor RUNX2, and RUNX2 promotes RANKL expression in tumor cells; these tumor cells then secrete RANKL to induce osteoblast differentiation into osteoclasts, and osteoclast-mediated bone tissue remodeling can expose HA and SPARC on the bone surface. BKCa and CXCL16 promote the aggregation and activation of  $\alpha V\beta 3$  and trigger the activation of downstream FAK. In addition to enhancing the activity of the ERK or PI3K pathway, activated FAK triggers cytoskeletal protein remodeling with the help of adaptor proteins, further enhancing tumor cell invasion ability. Cell information: The PC-3 cell line was initiated from the bone metastasis of a grade IV prostatic adenocarcinoma from a 62-year-old Caucasian male; DU145 was initiated from a 69-year-old Caucasian male with brain metastasis of prostatic adenocarcinoma; LNCAP was isolated from the left supraclavicular lymph node of a 50-year-old prostate cancer patient. LNCAP is sensitive to hormones; C4-2B is a subtype derived from the LNCAP cell line. **Abbreviations:** BSP, bone sialoprotein; VEGF, vascular endothelial growth factor; HA, hydroxyapatite; SPARC, osteonectin; FAK, focal adhesion kinase; IGF-1, insulin-like growth factor; IL-8, interleukin8; OPN, osteopontin; MMP (2 or 9), matrix metalloproteinase (2 or 9); CCN2, connective tissue growth factor; CCL2, chemokines2; CXCL16, chemokines16; P, phosphorylated; AC, acetylated.

microenvironment into a suitable site for survival.<sup>42</sup> For PCa bone metastasis, tissue reconstruction is inevitable after cancer cells arrive at bone. The osteoclast differentiation factor RANKL is an important regulator involved in bone metabolism. RANKL induces osteoblasts to differentiate into osteoclasts and initiates osteolysis.<sup>43</sup> Hydroxyapatite (HA) is exposed on the surface of the dissolved bone, and this structure promotes tumor cell immobilization on the bone surface via  $\alpha$ V $\beta$ 3.<sup>44</sup> Bongjun Kim et al confirmed that acetylated RUNX2 induces RANKL expression, and protein acetylation was attributed to the fact that integrin  $\alpha$ V $\beta$ 3 mediates CCN2-stimulated acetylation and stabilization of RUNX2 in highly bone-metastatic cancer cells (Figure 1).<sup>40</sup>

## Cellular Chemokines Can Enhance PCa Invasion by Regulating $\alpha$ V $\beta$ 3 Expression

Numerous cellular chemokines are related to malignant cell proliferation, survival, spread, and angiogenic response.<sup>45–50</sup> In resistant-prostate cancer, recrudescence cancer cell survival depends on autocrine chemokines that stimulate angiogenic and drug resistance processes.<sup>51–54</sup> Our previous study demonstrates that interleukin-8 (IL-8 or CXCL8) influences  $\alpha$ V $\beta$ 3 level in PC3 cells, and SB225002 (IL-8 receptor antagonist) potently attenuates cancer cell invasion and  $\alpha$ V $\beta$ 3 expression levels. These effects are regulated by the AKT/mTOR signaling pathway (Figure 1). In the SB225002-treated group, phosphorylated AKT is inhibited, and the expression levels of downstream proteins mTOR and P-mTOR were significantly reduced.

Chemokine 2 (CCL2) is another cytokine that is associated with tumor progression.<sup>55</sup> Functional CCL2 is a chemoattractant for monocytes, memory T-cells, and natural killer cells in adaptive immunity responses;<sup>56–59</sup> however, CCL2 has also been reported to be implicated in the regulation of cancer cell growth, angiogenesis, and metastasis in prostate and breast cancers.<sup>60,61</sup> Tien-Huang Lin et al used shRNA to silence CCL2 expression in PC3 cells and found that inhibition of CCL2 expression inhibited the migratory ability of PC3 cells by approximately 80%. Regarding the mechanism by which CCL2 regulates the PCa invasion, they verified the interrelation between CCL2 and  $\alpha$ V $\beta$ 3. Pretreatment of cells with an anti- $\alpha$ V $\beta$ 3 integrin monoclonal antibody markedly inhibited CCL2-induced PCa cell migration, and knockdown of CCL2 also reduced  $\alpha$ V $\beta$ 3 integrin expression in PC3 cells. In addition,

they also demonstrated how CCL2 affects  $\alpha$ V $\beta$ 3 expression using the PKC $\delta$  inhibitor rottlerin and c-Src inhibitor PP2. They confirmed that CCL2 enhances cell migration and  $\alpha$ V $\beta$ 3 expression through CCR2 receptors/PKC $\delta$  and/or the c-Src pathway in human PCa cells (Figure 1).<sup>62</sup>

In addition to the fact that  $\alpha$ V $\beta$ 3 directly enhances PCa invasion via chemokine-mediated processes, membrane dynamics are also involved in the migration of malignant tumors induced by chemokines.<sup>63–65</sup> Integrin  $\alpha$ V $\beta$ 3 directly interacts with the ECM. In addition, actin rearrangement also plays a key role in regulating cellular interactions with the ECM, such as motility and vesicular trafficking. No study has confirmed that  $\alpha$ V $\beta$ 3 directly contacts actin, but some studies have noted that ezrin serves as a connector to communicate  $\alpha$ V $\beta$ 3 signals to actin. Ezrin is a scaffold protein that promotes protein interactions with the actin cytoskeleton to regulate cell migration.<sup>66,67</sup> Especially in PCa, ezrin can connect the tail of the  $\beta$ -subunit in  $\alpha$ V $\beta$ 3 to actin.<sup>68–70</sup> In experiments assessing how CXCL16 affects PCa invasion, researchers found that treatment of PC3 cells with CXCL16 cause  $\alpha$ V $\beta$ 3 molecules to cluster together on the cell surface, and p-Ezrin and F-Actin levels were increased significantly. The phosphorylation of these proteins is most likely transmitted by  $\alpha$ V $\beta$ 3, especially  $\beta$ -subunits because FAK is recruited to sites of integrin clustering following integrin engagement and is activated through undefined mechanisms. Activated FAK stimulates its downstream target ERK, and the ERK signaling pathway is a common pathway for Ezrin phosphorylation.<sup>71</sup> All these findings suggest CXCL16 not only directly enhances  $\alpha$ V $\beta$ 3 expression but also transmit signals into cells via  $\beta$ 3-subunits to trigger cytoskeletal protein rearrangement to promote enhanced tumor cell migration (Figure 1).<sup>17</sup>

## VEGF Promotes PCa Bone Metastasis by Controlling $\alpha$ V $\beta$ 3 and SPARC Interactions

SPARC, which is also called osteonectin, is a component of the bone matrix that modulates cellular interactions with the extracellular matrix, exerting an adhesive, promigratory effect on cells.<sup>72–74</sup> Studies confirmed that high expression of SPARC in most of the tumors with a tendency for bone metastasis.<sup>75,76</sup> In PCa, Sarmishtha De et al treated tumor cells with different antagonists and conclude that tumor cells on the bone surface linked with SPARC exhibit  $\alpha$ V $\beta$ 3 expression. In addition,  $\alpha$ V $\beta$ 3 blockade resulted in inhibition of LNCaP cell migration to SPARC.

Meanwhile, VEGF produced by tumor cells through autocrine mechanisms enhances the binding of  $\alpha v\beta 3$  and SPARC. Antibody neutralization of VEGF inhibits  $\alpha v\beta 3$  activation and decreased SPARC conjugation. Thus, VEGF secreted by tumor cells not only enhances neovascularization but also participates in  $\alpha v\beta 3$  activation and conjunction with SPARC (Figure 1).<sup>77</sup>

## PI3K Signaling Pathway Activation is Essential for IGF-I Regulation of $\alpha v\beta 3$ Expression

Insulin-like growth factor-I (IGF-I) is implicated in the evolution of various neoplasias.<sup>78–82</sup> In PCa, considerable experimental and epidemiological evidence showed that cancer cells produce IGF-I via autocrine mechanisms and express IGF-I receptors (IGF-IR). IGF-I enhances PCa proliferation by increasing caryomitosis, and these effects could maintain LNCAP growth in medium without serum.<sup>82</sup> Meanwhile, in the process of tumor conversion, IGF-I transforms androgen-dependent PCa cells to an androgen-independent phase.<sup>83–85</sup> In terms of migration, researchers found that IGF-I stimulates PCa invasion by combining with IGF-IR. Blocking  $\alpha v\beta 3$  with monoclonal antibodies mitigates the effects of IGF-I. In cell proliferation experiments, IGF-I enhances AKT and ERK phosphorylation to promote the proliferation of DU145 PCa cells. On the basis of these findings, researchers used chemical antagonists LY294002 (PI3K antagonist) and UO126 (ERK antagonist) to pretreat DU145 cells. Then, IGF-1 was added to the medium. They found that LY294002 completely counteracted the effect of IGF-1 in DU145 cells, but UO126 did not affect IGF-I induced migration of DU145 cells. They concluded that the mechanism by which IGF-I enhances PCa invasion might depend on the upregulation of  $\alpha v\beta 3$  expression levels through the PI3K signaling pathway (Figure 1).<sup>86</sup>

## Ion Channel Proteins Take Part in PCa Migration Mediated by $\alpha v\beta 3$

BKCa is a large-conductance calcium-activated potassium channel that is mainly expressed in excitable cells. It modulates vasomotor and nerve excitability by regulating membrane potential and calcium signaling.<sup>87–89</sup> However, experiments performed by Cheng Du et al demonstrated that both BKCa mRNA and protein levels in PCa cells were increased compared with normal cells. BKCa overexpression strengthens the invasive ability of cancer cell.

To investigate mechanisms by which BKCa regulates invasion, immunofluorescence experiments were performed, and BKCa- $\alpha v\beta 3$  complex formation was observed. In addition,  $\alpha v\beta 3$  and BKCa were reciprocally immunoprecipitated by each other. As the important downstream protein of  $\alpha v\beta 3$ , FAK phosphorylation levels were increased after BKCa overexpression. To verify the direct relationship between BKCa and  $\alpha v\beta 3$ /FAK, a BKCa inhibitor (IBTX) and activator (NS1619) were used to block or enhance  $K^+$  flow. BKCa inhibition and activation result in enhanced or decreased PCa cell invasion, respectively. These agents did not affect the expression of  $\alpha v\beta 3$  and FAK. Moreover, FAK phosphorylation is only related to  $\beta$ -subunit regulation; thus, these researchers suggest that BKCa facilitates the coupling between integrin  $\alpha v\beta 3$  and FAK or recruitment of FAK to the transmembrane BKCa/ $\alpha v\beta 3$  integrin complex (Figure 1).<sup>90</sup>

In addition to the above factors that participate in the progression of PCa, many additional proteins or compounds enhance the invasion ability of PCa through the integrin pathway, for example, thyroid hormones (T4) and Gastrin-releasing peptide receptor (GRPR). These proteins regulate invasion generally via the same mechanism, namely enhancing  $\alpha v\beta 3$  expression and promoting  $\alpha v\beta 3$  aggregation on the cell surface or increasing  $\alpha v\beta 3$  activity. Thus, all of these proteins and compounds are not summarized here.

## Intercellular Signaling Pathway Stimulated by $\alpha v\beta 3$ Related to PCa Metastasis

Ligand combines with its receptor to trigger a series of cascade reactions in the cytoplasm to regulate cell biological behavior.<sup>91,92</sup> This theory is adapted for  $\alpha v\beta 3$ , which influences PCa metastasis. Ligand enhances or inhibits PCa behaviors through one or more downstream pathways transmitted by  $\alpha v\beta 3$ . In this section, we will summarize several well-known downstream proteins of  $\alpha v\beta 3$ .

## FAK is the First Signaling Molecule of $\alpha v\beta 3$ in the Cytoplasm

Focal Adhesion Kinase (FAK) belongs to a kind of tyrosine kinase.<sup>93</sup> This protein does not contain a transmembrane structure but harbors two autophosphorylation sites at tyrosine residues 397 and 925.<sup>94</sup> Integrin  $\alpha v\beta 3$  molecules on the cell surface assemble to activate FAK and transmit information to FAK by the  $\beta$ -subunit of its intercellular tail.<sup>15,94</sup> After binding to integrin, most

ligands transmit the signal to FAK through the  $\beta$ -subunit of integrin. Then, the signals of the FAK signaling pathway are transmitted to the cytoplasm to trigger the corresponding biological effect. The following uses androgens and EMT serves as examples to illustrate how FAK participates in integrin-mediated PCa metastasis.

Androgen is an important factor that regulates PCa growth and mediates metastasis through the integrin-FAK pathway. Gabriella Castoria and coworkers used murine fibroblasts to investigate how androgen-induced PCa migration. They found that NIH3T3 cells (mouse embryo NIH3T3 fibroblasts) treated with RI88I (synthetic androgen) exhibit rapid FAK Tyr397 phosphorylation. Tyr118-phosphorylated paxillin (the focal contact-associated protein) parallels tyrosine phosphorylation of FAK upon androgen stimulation of cells. Meanwhile, cytoskeletal protein remodeling can be detected within a few minutes after androgen treatment. Subsequently, the researchers performed immunoprecipitation and found that the androgen receptor (AR) in androgen-treated NIH3T3 cells rapidly interacted with filamin A (FlnA) at the cytoskeleton. AR-FlnA assembled with integrin  $\beta 1$  to form a tripartite complex, and knockdown of either integrin  $\beta 1$  or FlnA abolished Tyr 397 phosphorylation of FAK induced by androgen. Thus, these researchers conclude that the interaction between AR and FlnA is a key event for FAK activation, and paxillin tyrosine phosphorylation in androgen-stimulated cells further reinforces the role of the AR/FlnA interaction in androgen-mediated motility.<sup>95-97</sup>

In most cancers, the epithelial-mesenchymal transition (EMT) is a key event in metastasis. At the molecular level, the EMT is characterized by a decrease in the expression of epithelial markers, mainly E-cadherin, which is located on the cell surface of epithelial tissues, and an increase in the expression of mesenchymal markers, such as vimentin, a cytoskeleton protein associated with EMT initiation. It is worth noting that FAK expressed by tumor cells also participates in the EMT process. In A549 lung cancer cells and colorectal cancer cells, FAK can be activated by EGFR, and phosphorylation of FAK at Tyr397 can trigger signal transduction mechanisms, activate downstream signaling molecules, downregulate E-cadherin expression and upregulate vimentin expression. In PCa, EMT does not occur in some PCa cells but occurs in other, such as PC3 and DU145 cells. In *in vitro* experiments, DU145 and PC3 cells (bone and brain metastasis of prostate cancer cells, respectively) exhibited increased invasiveness and high FAK, FlnA and paxillin expression

compared with C4-2B and LNCaP cells, which express lower FAK, do not exhibit the EMT, and move more slowly than DU145 and PC3 cells in migration experiments. Drugs can be used to induce the EMT, for example nerve growth factor (NGF). NGF robustly induces the EMT in DU145 and PC3 cells more effectively compared with C4-2B cells. These phenomena demonstrate that differences in FAK expression in cells with different invasive capabilities highlight the role of FAK in the EMT process of PCa.<sup>96,98</sup>

FAK is closely related to PCa metastasis. High FAK expression in PCa often indicates the presence of the EMT phenotype or the tendency of cells to metastasize. As mentioned previously, ligand does not have the ability to directly activate FAK, but FAK activity is influenced by integrin.<sup>90</sup> Recent studies have indicated that  $\alpha\beta 3$  blockade by an antagonist, neutralizing antibody and siRNA inhibit FAK phosphorylation.<sup>90,99</sup> In addition, as the direct substrate of FAK, the P85 subunit of PI3K can be phosphorylation by FAK.<sup>90,100</sup> Thus, if external stimuli are transmitted to the intracellular pathway through  $\alpha\beta 3$ , FAK phosphorylation is an important intermediate hinge in this process (Figure 1).

## The $\alpha\beta 3$ /RUNX2/RANKL Pathway is Closely Related to Osteolytic Metastasis

We mentioned earlier that IGF promotes PCa invasion via the  $\alpha\beta 3$ /RUNX2/RANKL pathway. Thus, RUNX2/RANKL is another downstream protein of  $\alpha\beta 3$ . Pathologically, PCa bone metastasis is classified as an osteolytic disease.<sup>101</sup> Runx2 is a transcription factor that plays a key regulatory role in osteoblast differentiation.<sup>102,103</sup> DNA sequencing found that the receptor activator of nuclear factor  $\kappa B$  ligand (RANKL) contains a Runx2 binding site in the promoter region.<sup>40,104</sup> Thus,  $\alpha\beta 3$ -induced bone matrix dissolution likely depends on the delivery of Runx2 to the nucleus to promote RANKL transcription. In terms of mechanism, Aditi Gupta et al did not provide evidence that  $\alpha\beta 3$  could directly interact with Runx2, but they determined that  $\alpha\beta 3$  activates Samd5. Activated Samd5 subsequently transports Runx2 to the nucleus. In the nucleus, Runx2 guides the transcription of RANKL.<sup>34</sup> RANKL is subsequently secreted by tumor and induces multinucleated giant cells to differentiate into osteoclasts and remodel bone matrix.

## The Classical Signal Pathway Receives Information Transmitted by $\alpha\text{V}\beta\text{3}$

In addition to specific proteins that act downstream of  $\alpha\text{V}\beta\text{3}$ , numerous well-known signal pathways participate in signal transport initiated by  $\alpha\text{V}\beta\text{3}$ . The ERK pathway is one example. Two primary mechanisms are involved in  $\alpha\text{V}\beta\text{3}$ -mediated activation of ERK. In one mechanism, FAK recruits a series of adaptor proteins, such as growth-factor-receptor bound protein2 and CRK-associated substrate, and activates protein kinases, such as SRC-family kinases, to activate ERK.<sup>99</sup> In another mechanism,  $\alpha\text{V}\beta\text{3}$  colocalizes with growth factor receptors on the surface of cells, and growth factors activate the ERK pathway.<sup>105</sup> The alternating process of contact and separation between the cell membrane and the ECM maintains tumor cells' movement on the ECM. ERK activation reduces cell adhesion to the ECM and guarantees that the cell membrane is prepared for the next contact. Activated ERK phosphorylates myosin-light-chain kinase (MLCK), and MLCK is a key regulator of contractile force within the cell. Phosphorylated MLCK activates the ATPase of myosin II. Myosin II provides energy for cells to move in the direction of actin contraction, and activated myosin generates contractile forces that pull the cell forward towards newly formed integrin contacts and breaks adhesive contacts at the trailing edge of the cell.<sup>106</sup>

PI3K is another transmitter of  $\alpha\text{V}\beta\text{3}$  signals. At the beginning of invasion, ligand combines with  $\alpha\text{V}\beta\text{3}$ , and the biological signal arrives at PI3K through  $\beta$ -subunit/FAK. Then, the PI3K/AKT/mTOR pathway induces transcription of MMPs and SIBLINGs.<sup>55,107</sup> These two families of proteins translocate to the cell surface and combine with  $\alpha\text{V}\beta\text{3}$ . MMPs hydrolyze collagen in the ECM, and SIBLINGs aid in tumor cell adhesion and organization.

The factors mentioned above are reported in the literature as mechanisms by which  $\alpha\text{V}\beta\text{3}$  guides PCa metastasis. However, in other malignant diseases, some small molecules are also important for the intracellular transport of the  $\alpha\text{V}\beta\text{3}$  signal, such as the adaptor protein CAS, SHC and small G proteins.<sup>108–110</sup> Some of these proteins are directly used as downstream messengers of  $\alpha\text{V}\beta\text{3}$ . Some require the help of a middle messenger. Further research on the role of these factors in PCa will provide more comprehensive mechanistic information on PCa invasion and metastasis.

## $\alpha\text{V}\beta\text{3}$ -RGD Specific Recognition Acts as a Tool for PCa Diagnosis and Therapy

Based on the highly specific expression of  $\alpha\text{V}\beta\text{3}$ , researchers have exploited various methods based on  $\alpha\text{V}\beta\text{3}$ -specific recognition of RGD sequences in the diagnosis and imaging of PCa. Kongzhen Hu et al linked 4-nitrophenyl-<sup>18</sup>F-fluoropropionate (18F-NFP) and  $\beta$ -glutamate-RGD with PEG to construct an  $\alpha\text{V}\beta\text{3}$  radiotracer. PET imaging systems are used to detect <sup>18</sup>F-FP-PEG2- $\beta$ -Glu-RGD2 uptake to assess the efficiency of implanted tumors in mice. The results showed <sup>18</sup>F-FP-PEG2- $\beta$ -Glu-RGD2 was rapidly cleared from blood predominately by renal excretion. MicroPET-CT imaging with <sup>18</sup>F-FP-PEG2- $\beta$ -Glu-RGD2 revealed high tumor contrast and low background in PC3 prostate cancer-bearing mouse models. <sup>18</sup>F-FP-PEG2- $\beta$ -Glu-RGD2 exhibited good stability in vivo. These experiments use  $\alpha\text{V}\beta\text{3}$  as the detection object and demonstrate that specific  $\alpha\text{V}\beta\text{3}$ -ligand binding can effectively detect the spread of cancer cells in the body.<sup>111</sup> Ambros J. Beer and their team further compared the sharpness of [<sup>18</sup>F] Galacto-RGD and bone scintigraphy in the diagnosis of PCa bone metastases. The diagnosis rate of patients with bone metastasis using [<sup>18</sup>F] Galacto-RGD is 78% (58 of 74 patients were diagnosed with bone metastases), but the image clarity of [<sup>18</sup>F] Galacto-RGD is significantly lower than that of bone scintigraphy. Researchers used a method based on [<sup>18</sup>F] Galacto-RGD tracking  $\alpha\text{V}\beta\text{3}$  imaging to demonstrate that image clarity is closely related to the expression level of  $\alpha\text{V}\beta\text{3}$  in the tumor. Compared with the bone scintigraphy method, the use of [<sup>18</sup>F] Galacto-RGD to diagnose bone metastases in patients with PCa has the advantages of a good visualization and low background of surrounding tissues.<sup>112</sup>

In addition to galactose-labeled RGD, researchers also use <sup>99m</sup>Tc, bombesin, gastrin-releasing peptide receptor and RGD labeled with Afterglow materials to track PCa progression.<sup>113–115</sup> According to their results, after chemical- or biomarker-labeled RGD combines with  $\alpha\text{V}\beta\text{3}$ , the signal can be visualized in vitro using equipment to clearly distinguish the lesion from the surrounding tissue. This conclusion indicates that clinicians can judge the progression of PCa by detecting the expression of  $\alpha\text{V}\beta\text{3}$  and its location in patients and can predict whether the tumor is at risk of bone metastasis if necessary.

Inspired by RGD's specific binding to  $\alpha\text{V}\beta\text{3}$ , researchers have also developed new PCa treatment options. Traditional chemotherapeutic drugs have a short half-life and are often present at insufficient concentrations when

they reach the treatment site, which seriously affects the therapeutic effect of the drug. Docetaxel (an  $\alpha\beta3$  antagonist) is a widely used anticancer drug that is used alone or in combination with other drugs to treat tumors.<sup>116</sup> However, this drug suffers from the limitations of nonspecific cytotoxicity in normal tissues. To improve the tissue specificity of this drug, Hitesh Kulhari M Pharm et al used nanomicelles to couple docetaxel and RGD sequences and successfully achieved RGD- $\alpha\beta3$  targeted drug delivery.<sup>117</sup> Yajie Gao et al successfully coupled paclitaxel to RGD to achieve a drug delivery model for mouse xenografts.<sup>118</sup> Both of these targeted drug delivery methods show increased therapeutic efficiency and reduced cytotoxicity than traditional drug delivery methods, while chemically modified drugs exhibit increased stability in vivo. In addition to the direct coupling of RGD and drugs, researchers still use liposome-encapsulated drugs to couple RGD for targeted drug delivery experiments to reduce the degradation of chemotherapeutics. In experiments using liposomes to encapsulate cisplatin, liposomes showed significantly increased cellular uptake and increased cytotoxicity of loaded cisplatin. Clinical observation confirmed that the RGD-conjugated liposomal drug system could inhibit osteoclastic and osteoblastic bone lesions, relieve pain, and improve overall survival.<sup>119,120</sup>

Another novel treatment strategy is RGD-mediated oncolytic virus targeting PCa. Oncolytic adenovirus was able to selectively replicate and kill cancer cells while sparing normal cells.<sup>121,122</sup> The anti-tumor efficiency of this virus depends on the level of Coxsackie virus adenovirus receptor (CAR) expression by tumor cells.<sup>123</sup> Experimental results by Yue-Hong Shen et al revealed that the E1A/E1B double mutant oncolytic adenovirus AxdAdB-3 exhibited antitumor activity in an orthotopic PCa SCID (severe combined immunodeficiency) mouse model. However, AxdAdB-3 showed insufficient cytopathic effects in some PCa cell lines that expressed low levels of CAR. To overcome the low treatment efficiency caused by low expression of CAR, they insert the RGD peptide into AxdAdB-3 to form a new oncolytic virus: AxdAdB3-F/RGD. They used the novel oncolytic virus to infect PCa cells in vitro, and a PCa xenograft model was constructed using nude mice. AxdAdB-3 was more cytopathic in CAR-positive PCa cells compared with CAR-negative cells, whereas AxdAdB3-F/RGD caused potent oncolysis in both CAR-positive and CAR-negative cancer cells. In contrast, AxdAdB3-F/RGD was not cytopathic against

normal prostate epithelial RWPE-1 cells. Intratumoral injection of AxdAdB3-F/RGD into CAR-negative prostate cancer cell xenografts in nude mice can significantly inhibit tumor growth.<sup>124</sup>

## Conclusion

Prostate cancer recurrence and mortality are increasing rapidly. The identification of an effective anti-tumor strategy is crucial to improve patient prognosis and prolong patient survival. The relationship between integrin  $\alpha\beta3$  and prostate cancer is gaining increasing attention. As a transmembrane protein,  $\alpha\beta3$  is involved in almost all prostate cancer progression processes. Different ligands combined with  $\alpha\beta3$  mediate various biological behaviors of tumors, such as proliferation, invasion, migration, angiogenesis and immune escape. Based on this characteristic of  $\alpha\beta3$ , multiple diagnostic and therapeutic strategies have been developed to combat prostate cancer. Here, we summarized the current role of  $\alpha\beta3$  in the progression of prostate cancer and new treatments developed for  $\alpha\beta3$  as a therapeutic target. Although these methods show high detection rates and therapeutic effects, the safety of the corresponding reagent or drug needs to be further confirmed. The identification of a safe, effective, and inexpensive antitumor drug is important for prostate cancer patients.

## Disclosure

Meng Xu is an employee of Seekgene Technology Co., Ltd. The authors report no other possible conflicts of interest in this work.

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