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Original Article

Hylonome

Integrins in bone recognition and metastasis

T.V. Byzova

JJ Jacobs Center for Thrombosis and Vascular Biology, Taussig Cancer Center,
Lerner Research Institute, Cleveland, Clinic Foundation, Cleveland OH, USA

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Many of the major non-collagenous proteins of bone matrix are recognized by the integrin family of adhesion receptors. Integrins mediate cell adhesion, spreading and migrating to bone matrix and also trigger intracellular signaling cascades, which regulate responses ranging from apoptosis to gene expression. Bone-specific non-collagenous matrix proteins include bone sialoprotein, osteopontin and osteonectin (SPARC).

Highly phosphorylated bone matrix protein bone sialoprotein (BSP) contains a RGD sequence and is recognized by several integrins, including αvβ3 and αvβ5. RGD-containing peptides inhibit these interactions and block cell adhesion to BSP. BSP is recognized as an important ligand for αvβ3 integrin in processes ranging from bone formation to the homing of metastatic tumor cells. We demonstrated that recognition of BSP is regulated by an activation state of αvβ3 integrin. Stimulation of lymphocytes or osteoblasts with model agonists markedly enhances αvβ3–dependent cell adhesion to BSP. Osteonectin or SPARC (secreted protein, acidic and rich in cysteine) is also a component of bone matrix that is believed to play an important role not only in bone development but also in tumor biology and metastasis, since it is often called "pro-invasive" protein. We have shown that tumor cell migration to SPARC is mediated by αvβ3 and αvβ5 integrins and is controlled by an autocrine loop in which VEGF engages VEGFR-2. We found that SPARC is a key protein that attracts prostate cancer cells to bone. SPARC-deficient bone extracts support minimal migration of prostate cancer cells and addition of purified SPARC restores the rate of the cell migration.

We found that both bone matrix proteins, BSP and SPARC, are able to influence the VEGF signaling in tumor cells. BSP, purified SPARC and recombinant SPARC increased VEGFR2 expression. Adhesion of prostate cancer cells to SPARC also induced VEGF production, and this increase was completely inhibited by anti-αvβ3 and αvβ5 blocking peptide cRGDfv. We verified this finding using a second prostate cancer cell line PC3. Importantly, the upregulation of VEGF production by SPARC via αvβ3 and αvβ5 is a prostate cancer-specific phenomenon, which provides prostate cancer cells with significant growth advantage in bone tissue.

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Corresponding author: Tatiana Byzova, Ph.D., Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195, USA
E-mail: byzovat@ccf.org

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