MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

40007, Sumy, 31 Sanatorna St.
e-mail: EUMJ@med.sumdu.edu.ua
http://eumj.med.sumdu.edu.ua
ISSN: 2663-5909 (print)

DOI: https://doi.org/10.21272/eumj.2019;7(2):96-108

Abstract **УДК 616.65-008.857:616.71]-006.6-033.2**

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MOLECULAR ASPECTS OF THE BONE METASTASTASES DEVELOPMENT IN PROSTATE CANCER

This review is devoted to the topical issue of modern medicine – the molecular mechanisms and factors for the development of bone metastases of malignant tumors, in particular prostate cancer. The recent publication on the formation and progression of prostate cancer bone metastases were analyzed in this study.

The expression of some molecular markers in tumor and metastatic tissue and their role in tumor progression were also analyzed in this study. A common concept for the development of specific metastases is a *seed and soil* theory. According to this concept, circulating cancer cells recognize some organs as the optimal microenvironment for their development. However, the molecular mechanisms of this phenomenon remain unknown.

Molecular and genetic features of the androgen receptors expression in the tumor and their role in metastatic tissue were summarized and compared in this study. We also demonstrated the effect of these receptors on the development of osteoblastic metastases and castration-resistant prostate cancer. Authors analyzed and summarized data about the role of p53 protein, Bax and activated caspase 3 in apoptosis, mechanisms of neoangiogenesis and remodeling of tumor connective tissue with matrix metalloproteinase 1, the presence of collagen type I and osteonectin in neoplastic tissues and the role of inflammation in metastasis development. Functions of heat shock proteins with molecular masses of 70 and 90 kDa and their role in tumor and metastatic tissue were also analyzed. Thus, the study complements and summarizes the data on the development of bone metastases of prostate cancer. The study analyzed the molecular characteristics of prostate cancer during its metastatic spread.

Keywords: prostate cancer, bone metastases, immunophenotype, androgen receptors, neoangiogenesis, heat shock proteins, matrix metalloproteinase 1, inflammation, osteoblastic markers, apoptosis.

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Резюме

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МОЛЕКУЛЯРНІ ОСОБЛИВОСТІ РОЗВИТКУ КІСТКОВИХ МЕТАСТАЗІВ РАКУ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ

Представлена робота присвячена актуальному питанню сучасної медицини – молекулярним механізмам та факторам розвитку кісткових метастазів злоякісних пухлин, зокрема раку передміхурової залози. У ході дослідження були проаналізовані положення літературних джерел останніх років щодо процесів формування кісткових метастазів раку передміхурової залози та експресії окремих марке-

рів у її тканині. Зокрема було всебічно розглянуто класичну концепцію *seed and soil*, котра описує феномен тропності циркулюючих метастатичних клітин до певного мікрооточення та викликає розвиток специфічних за локалізацією метастазів.

Були узагальнені та порівняні погляди на молекулярно-генетичні основи впливу експресії андрогенових рецепторів неопластичних клітин на розвиток саме остеобластичного типу метастазів, причини та молекулярні механізми розвитку кастраційно-резистентного раку передміхурової залози. Автори розглянули та узагальнили теоретичні знання, що описують участь білків p53, Bax та активованої каспази 3 в апоптозі, процеси неоангіогенезу та ремоделювання сполучнотканинного компоненту пухлин із залученням матриксної металопротеїнази 1, особливості присутності колагену 1 типу та іншого остеобластичного маркеру остеонектину в неопластичній тканині та роль запалення у процесах метастазування. Також було висвітлено функції білків теплового шоку із молекулярними масами 70 та 90 кДа та їх роль у пухлинній та метастатичній тканині.

Таким чином проведене дослідження доповнює та узагальнює дані, що стосуються процесів розвитку кісткових метастазів раку передміхурової залози. У ході дослідження було всебічно проаналізовано молекулярно-генетичні особливості раку передміхурової залози за його метастатичного поширення.

Ключові слова: рак передміхурової залози, кісткові метастази, імунофенотип, рецептори до андрогенів, неоангіогенез, білки теплового шоку, матриксна металопротеїназа 1, запалення, остеобластичні маркери, апоптоз.

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Вступ

Peculiarities of prostate cancer bone metastases

Prostate cancer (PC), as well as breast cancer, is characterized by pronounced osteotropism regarding metastases. It is known that approximately 80% of metastases to the organs of the locomotor apparatus occur due to these pathologies [1], while malignant tumors of other localizations do not have such tropism [2; 3]. The first person, who tried to explain this phenomenon, was the English surgeon Stephen Paget, who believed that tumor cells are able to "colonize" only those organs, which have a favorable microenvironment for neoplastic cells. This theory is still relevant for tumors that form distant metastases [4].

In 1928, James Ewing suggested that the morphological characteristics of blood and lymphatic vessels have a decisive influence on the peculiarities of tumor metastasis [4].

It is now believed that such characteristics of the red bone marrow as high degree of vascularization, presence of a significant number of biochemical factors (cell adhesion molecules, cytokines and chemokines) in conjunction with physical factors (low pH, hypoxia, high calcium content in the extracellular matrix) contribute to the colonization, survival and growth of tumor cells in bone tissue [5; 6].

The vast majority of prostate cancer bone metastases are sclerotic, whereas for other malignancies (breast cancer, kidney and lung cancer) metastases are predominantly osteolitic in nature [7; 8]. Despite the fact that PC bone metastases may result in osteogenesis, the newly formed bone tissue has impaired histoarchitectonics and contributes to the appearance of pathological fractures [9].

During metastases of neoplastic PC cells to the bone tissue they first cause bone resorption, which leads to the release of significant amounts of biologically active substances and growth factors, in particular insulinlike growth factor (IGF) 1, and

stimulates the activity of osteoblasts [10; 11]. It has also been shown that prostate cancer increases serum level of endothelin-1, which stimulates the proliferation of osteoblasts and promotes osteogenesis [12; 13].

Experimental in vivo studies have shown that bone mass reduction significantly decreases the likelihood of PC bone metastases development [14]. There is also indication of the possibility of activation of osteblasts by cancer cells through bone morphogenetic protein 1 [15]. There is an assumption that urokinaselike plasminogen activator, just like prostate-specific antigen (PSA) produced by the tumor is capable of activating osteoblast through hydrolysis of IGF-binding proteins, resulting in increased levels of free IGF. PSA is also able to cleave parathyroid hormone bound protein, which is the promoter of osteoclastogenesis, reducing bone resorption [16; 17; 18].

It is known that sex hormones influence bone growth and development [19; 20]. Thus, men with low androgen levels show bone mass reduction similar to women in menopausal period [21].

Sclerotic character of PC bone metastases in comparison with malignant neoplasms of other localizations also indicates association with androgens, expression of which can be found in osteoblasts [22]. They are important in maintaining the mass of the trabecular bones, and are able to indirectly inhibit osteoclastogenesis through inhibition of the expression of nuclear factor kV activator receptors in osteoblasts [23; 24]. Androgens are also capable of converting to estrogen with the activation of its receptors in osteoclasts and osteoblast precursors. All described mechanisms cause inhibition of bone resorption and stimulation of osteoprotegerin synthesis in osteoblasts. Men with low levels of androgens show a bone mass reduction similar to women in menopausal period [25]. However, the results of studies, conducted by many laboratories, differ significantly, not providing a complete picture of the initiation and progression of PC bone metastases. That is why the aim of this study was to analyze the literature data and characterize the molecular genetic peculiarities of PC bone metastases development.

Sensitivity to steroid hormones

Androgens are necessary for the normal development and functioning of unaltered prostate, as well as the vital activity of PC cells [26]. Their action is conditioned by the activation of androgen receptors, which are ligand-dependent transcription factors. Testosterone, which has the highest concentration in blood plasma, is secreted by Leydig's cells in the testicles and in a small amount (up to 5-10 %) by the adrenal glands [27; 28; 29]. In prostate tissue testosterone is converted into dehydrotestosterone, a steroid hormone, that has more pronounced effects [30]. When androgens interact with the corresponding receptors, the processes of their dimerization and transport from the cytoplasm to the nucleus are activated. Activation of various genes, such as KLK2, NKX3-1, STEAP2 and KLK 3, which encodes PSA synthesis, occurs as a result of binding of receptor dimers to the corresponding promoter sites of target genes. There is also possible interaction with numerous coregulatory proteins, like HOXB13 and FOXA1 [31].

Prostate cancer is a hormone-dependent disease, so the androgen receptors is the primary molecular element of the systematic treatment of this disease. However, patients with advanced 3C have tumor progression and development of castration-insensitive prostate neoplasia [32; 33; 34]. That is, the level of PC sensitivity to androgens is proportional to the degree of its differentiation. However, the production of enzymes for the synthesis of androgens continues in the tissue of androgen-independent PC, as a result their concentration in tumor tissue may exceed normal level [35].

This hormonal resistance is explained by changes in androgen receptors, including hyperexpression of proteins that are part of androgen receptors (AGR), amplification and mutation of AGR genes, as well as the formation of so-called AGR variants, or isomers [36]. These isomers are fragments of the AGR-proteins, not capable of binding to AGR domains. Although these molecules were found in the castration-resistent PC, they do not have a significant effect on the function of the unaltered prostate or in primary tumors of this gland [37].

However, today the possibility of a combined effect of androgens and estrogens on the prostate carcinogenesis processes has been proved. Age-related involutive changes in the reproductive system of men lead to impairment of androgens and estrogen ratio: the level of androgens is reduced with age, while estrogen level remains constant or even increases [38]. Activation of estrogen receptors (ER) α in an unaltered prostate leads to increased proliferative activity of glandular epithelium and inflammation. Instead, activation of ERß has antiproliferative and even carcinosuppressive effect, and its expression changes dynamically during

prostate cancer progression [39; 40]. Although the expression of these receptors to estrogen in the tumor microenvironement is reduced compared to unaltered prostate tissue, higher levels of ERα expression were detected in the stroma of highly differentiated tumors, compared to low differentiated [41]. R. Pisolato et al. (2016) established not only the possibility of formation of new ER isoforms, but also the variability of their localization, which can influence the activation of ERK1/2 signal pathway in the prostate cancer RS-3 cell line [42].

Osteoblastic markers in PC

Osteonectin (OSN) (SPARC, a basal membrane protein, BM-40) is a calcium-binding matrix protein with a molecular mass of 32 kDa. [43; 44]. It is a glycoprotein with a spiral spatial structure, capable of variable glycosylation depending on tissue-specific expression [45; 46].

At one time OSN was considered to be the main marker of biomineralized soft tissues due to its pronounced concentration in the calcification foci. However, studies, conducted by J J.D. Termine et al. (1981) demonstrated a much broader model of its expression in both mineralized and non-mineralized tissues [47]. Typically, OSN expression is associated with the presence of fibrillar collagens, such as type I collagen. The structure of OSN consists of binding domains with both collagen and hydroxyapatite [48; 49]. So, collagen-binding domain is localized in the C-fragment of the OSN molecule, whereas the hydroxyapatitetropic is located in the N-region. This creates the conditions for its participation in the processes of collagen mineralization both during osteogenesis and biominerogenesis [47]. OSN functions also include regulation of cell proliferation and migration, tissue remodeling and angiogenesis [50; 51].

In addition to osteoid cells, other types of cells, present in mineralized tissues, including endothelial cells and fibroblasts, demonstrate the ability to synthesize OSN [52]. OSN can also be found in platelets and macrophages in the foci of chronic injury, as well as in endotheliocytes [53; 54; 55].

Today, the question of OSN participation in the initiation and progression of prostate cancer is insufficiently studied, since most of the works are aimed at studying its action on the bone tissue elements. In the case of PC, OSN has a predominantly stimulating effect and causes further progression of prostate neoplasia [56], thus increasing the aggressiveness of the tumor and its metastatic potential. According to Ruela-Arispe M. L. et al. (1995), this phenomenon is explained by the fact that OSN is able to disrupt the morphology of target cells by reducing the number of focal intercellular contacts and blocking cell adhesion to basal membranes or surrounding cells. The study has revealed the absence of OSN in the tissue of unaltered prostate and its expression in neoplastic cells and extracellular matrix in 30% of PC cases [57].

The studies of N. Burns-Cox et al. (2001) showed significant changes in the protein content in the stromal component of the tumor in PC: with the increase in the PC stage according to Gleeson, the collagen content (in particular type I collagen) decreases, while in the surrounding unaltered prostate tissue, this indicator significantly increases compared to the control. However, there is a significant intensification of expression of collagen synthesis markers in the prostatic neoplasia foci [58].

There is also an indication of the OSN ability to increase the production of matrix metalloproteinases, which indirectly influences the processes of PC bone metastases, where its increased expression is also manifested [59].

The role of matrix metalloproteinase 1 in PC progression

Matrix metalloproteinase 1 (MMP1) belongs to zinc-containing endopeptitases with pronounced collagenase activity [60; 61]. Synthesis of this enzyme occurs both in neoplastic cells and in tumor stroma and is associated with tumor progression, prognosis deterioration, invasion and shortening of survival time [62]. Its ability to influence epithelial-mesenchymal transformation of tumor cells and modulate intercellular interactions also significantly influences invasive potential of the tumor [63; 64; 65]. It has been demonstrated that inhibition of MMP1 synthesis by bone morphogenetic protein 6 reduces the likelihood of metastases [66]. The ability of MMP1 to interact with PAR1 and MAPK determines its role in the processes of cell invasion, angiogenesis and dissemination [67].

MMP1 along with ADAMTS-1 (EGF-like growth factor) is considered as a predictor of osteolysis, which corresponds to the development of bone metastases [68]. In their studies, Casimiro S. et al. (2013) revealed a relationship between the expression of MMP1 and RANK (activator of NF-κB receptors) via ERK/cFos and JNK/cJun and MMP1 promoter activation. Disabling of these pathways leads to a decrease in the number of osteoclasts and the intensity of osteolysis. This indicates that PC cells synthesize MMP1, which

stimulates the development of metastatic phenotype of tumor cells [69; 70].

Heat shock proteins and CP

Heat shock proteins (HSP) are a group of chaperone proteins that take part in the spatial organization of the protein and maintain its structure during stress, preventing their aggregation [71; 72]. At the moment, the most studied are HSPs with a molecular weight of 70kDa and 86kDa (Hsp70 and Hsp90, respectively), which play a significant role in the processes of proliferation, differentiation and carcinogenesis [73]. Their participation in carcinogenesis and influence on immune response modeling, apoptosis inhibition and development of resistance to chemotherapeutic agents has led to their thorough study [74]. Blocking of apoptosis is achieved by binding of high-molecular HSPs with caspases and impairment of their activation. This creates conditions in the tumor tissue for the accumulation of a pool of cells with hidden mutations and further tumor progression [75].

The relationship between the expression of HSPs in epithelial malignant tumors and the deterioration of prognosis for the patient is also indicated [76]. In their study, Li Ni et al. (2010) proved the participation of Hsp90 in the process of implementation of the effects of androgens in PC tumor cells through creation of superchaperone complex FKBP51-Hsp90-p23. This complex binds with AGR and increases the number of these molecules in the cytoplasm, stimulating androgendependent transcription and cell growth, and reduces Hsp70 concentration [77; 78]. Toshifumi Kurahashi et al. (2007) disproves relationship of Hsp70 and Hsp90 and PC progression. Instead, he thinks that low-molecular-weight HSPs, such as Hsp27, can be used as a predictor of biochemical recurrence in patients after radical prostatectomy [79].

Although HSPs are unable to directly influence the processes of biomineralization, protein conglomerates, in which they are present, are able to indirectly influence the biomineralcreation process in the human body. Shifa Narula et al. (2017) proved the presence of Hsp70 as a matrix protein in the urinary system calculi [80]. There is also indication of the involvement of this protein and osteopontin in the processes of crystal structure modeling of the biominerals, reducing their cytotoxic effect [80; 81]. According to Erman Chen et al. (2015) Hsp70 directly affects the differentiation of mesenchymal stem cells and is able to stimulate osteogenesis in them. This effect is implemented through the activation of alcaline phosphatase and ERK-dependent signaling pathway at its extracellular concentrations exceeding 200 ng/ml [82].

However, Fong-Ngern K. et al. (2016) pointed out a direct involvement of Hsp90 in the development of urolithiasis. This protein is expressed on the apical surface of the tubular epithelium and promotes the binding of calcium oxalate to epithelial cells by means of a specific Ca2+-binding domain in its structure. Moreover, Hsp90 has been detected on the surface of endocytic vesicles during internalization of calcium crystals, which indicates its involvement in this process [83]. This macromolecule takes direct part in an intracellular calcium homeostasis. The interaction of a specific ATP-binding domain in the Hsp90 molecule leads to a decrease in the amount of intracellular ATP and a decrease in the passage of Ca^{2+} through protein kinase C and membrane calcium transport proteins (4^{th} isoform). This results in an increase in the concentration of calcium inside the cell [84].

However, low-molecular HSPs may have the opposite effect in the bone tissue – dephosphorylated Hsp27 inhibits osteocalcin, thereby reducing the intensity of mineralization processes in mature osteoblasts [85].

Apoptosis and angiogenesis in prostate cancer tissue

The process of apoptosis activation can be both internal and external [86]. The external apoptotic pathway is activated by TNF receptors (Fas, TRAIL). According to this mechanism, the caspase 8 activates the caspase pathway with the involvement of caspase 3, 6 and 7, which causes apoptosis [87]. The internal (mitochondrial) pathway is Bcl-2-dependent and can be initiated by DNA damage, oxidative stress, dysfunction of growth factors, etc [88; 89].

Protein p53 is a tumor suppressor due to its ability to regulate the transcription of proapoptotic factors and thus initiate cell apoptosis through multiple pathogenetic pathways, in particular through the cell cycle termination. This protein can interact with Bax protein and predetermine increased permeability of the outer mitochondrial membrane [90; 91]. However, the presence of mutated R53 protein in the cell leads to dysfunction of the wild type of this protein. Thus, changes in the expression of this protein lead to disruption of the cell cycle, accumulation of neoplastic cell mutations and cancer progression [92]. It was shown that the deficiency of functional p53 in tumor cells significantly reduces the effectiveness of radio- and chemotherapy, and

consequently worsens the prognosis of the disease [93].

Activated caspase 3 (Casp3) is one of the key enzymes, involved in apoptosis. In its inactive state, this protein has a mass of 32 kDa. However, in case of its activation by means of aspartate pathway due to a cascade of biochemical transformations, P12 and P17 subunits are created, which form the activated enzyme [94]. Thus, the detection of the activated form of Casp3 can be used to assess the levels of apoptosis in tissues [95]. In case of apoptosis activation via internal pathway (involving proteins from the bcl-2 family), occurs activation of Casp3 with the involvement of cytochrome C and Apaf-1 with the formation of the complex – apoptosome [96].

Bax protein (or Bcl-2 associated X-protein) is related to Bcl-2 associated proteins. Its activation is accompanied by its conformational changes, destabilization of the mitochondrial membrane by the formation of transmembrane pores, release of cytochrome C to the cytoplasm and activation of oxidative phosphorylation, as well as impairment of intracellular calcium homeostasis [97; 98]. That is why it is considered as a key link of both apoptotic processes and necrosis [99]. In addition, Bax is able to indirectly stimulate apoptosis processes by activating caspase of the 3-dependent apoptotic pathway [100]. Its proapoptotic activity can also be mediated due to its ability to inhibit antiapoptotic genes, such as Bcl-2 and Bcl-XL [101]. Thus, the Bcl-2/Bax system can become a potential therapeutic link in the management of malignant tumors by stimulating the apoptosis of neoplastic cells [102; 103]. It was also reported about the possible therapeutic effect of Bax expression stimulants in the treatment of paclitaxel-resistant breast cancer by the means of binding to Bcl-XL and inhibiting its antiapoptotic action [104]. However, no studies were conducted regarding the influence of itraluminary inclusions on the level of Bax expression in prostate cancer tissues and its participation in the processes of metastasis.

Angiogenesis is an important part of tumor growth and progression. Earlier, an increased expression of vascular endothelial growth factor (VEGF) in PC tissue was established [105]. Its role in the processes of proliferation of endotheliocytes, vascular growth, initiation of carcinogenesis and metastases has been established [106; 107; 108]. Combination of these effects is implemented by means of interaction of several forms of this factor (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and PIGF) with tyrosine kinase receptors (VEGFR-1, VEGFR-2 and VEGFR-3) [109; 110]. From the perspective of carcinogenesis and PC metastasis, the most important is the interaction of VEGF-A–VEGFR-2. As a result of this interaction, there is a cascade of intracellular phosphorylation reactions, which result in cell proliferation, their migration and survival, as well as pronounced angiogenesis. This is conditioned by the activation of molecular mechanisms PI3K, Akt/PBK, NF-κB, p38MAPK, RAS, MAK and ERK [111]. *In vivo* studies have shown that VEGF in bone tissue has auto- and paracrine action. It participates in chemotaxis, proliferation and differentiation of osteoblasts, modulation of osteolytic function of osteclasts [112]. The presence of metastatic PC tissue with high VEGF-synthesizing function creates an imbalance between the processes of resorption and formation of bone tissue with a predominance of the latter, which is manifested by development of osteoblastic (osteosclerotic) metastases [113; 114]. Thus, expression of VEGF by neoplastic tissue creates optimal conditions for the formation of osteosclerotic PC metastases, stimulates and supports the growth of cancer cells, initiates angiogenesis and has a transforming effect on the tumor tissue itself [111].

The role of inflammation in the development of bone metastases

The role of inflammation in the development and progression of prostate cancer due to DNA damage (genetic and epigenetic modulation), stimulation of cell proliferation and angiogenesis, cytoskeleton and extracellular matrix remodeling is proven [115; 116]. However, there is another potential impact of inflammation on the PC metastasis.

Initiating stage of the process of PC metastasis is the epithelial-mesenchymal transformation – morphological transformation of cells due to reduction of synthesis of cell adhesion molecules [117]. As a result, tumor cells acquire characteristics that allow them to migrate from the focus of the primary tumor and cause their intravasation [118]. This process requires the presence of $CD68^+$ tissue macrophages. Earlier, it was found that their increased number corresponds to the worst PC prognosis [119]. Synthesis of mediators of inflammation and cytokines, such as TNFα, by macrophages and neutrophils causes the development of reactions of NF-κB cascade mechanisms, which leads to inhibition of E-cadherin synthesis and increase of metastatic potential of tumors [120]. NF-κB nuclear factor is also associated with the release of IL-6 cytokine [121].

During inflammation endothelial cells express a number of cell adhesion molecules, in particular the P- and E-selectins, intracellular adhesion molecules A and vascular adhesion molecules 1. These proteins are ligands of K (C-X-C) (CXCR) 4/6/7 (CXCR4/6/7) chemokines, αvβ3 integrin, RANK, CD44 and annexin 2, expressed by neoplastic cells. The interaction of these substances allows cancer cells to bind specifically to endotheliocytes, accelerating their migration and attachment to endotheliocytes of bone tissue vessels [122]. This creates conditions for the "recognition" and attachment of freely circulating tumor cells to the tissue that best corresponds to the immunophenotype of these cells, has an optimal microenvironment and creates conditions for the growth and development of metastases [123].

Conclusion

Thus, the development of PC bone metastases is a complex process, which is caused by the biochemical peculiarities of both tumor cells and bone tissue microenvironment. The process of metastasis is accompanied by a cascade of biological reactions, involving a variety of pathological pathways and biological interactions.

Financial support

This study was carried out in the framework of the research topic of the Department of pathological anatomy of SSU No. 117U003937 "Development of a method for diagnosing tumors of the reproductive system using cell adhesion molecules of cancer-embryonic antige".

Conflict of interests

The authors declare no conflict of interests.

References (список літератури)

1. Coleman RE. Skeletal complications of malignancy. *Cancer*. 1997;80:1588–1594.
2. Bussard KM, Gay CV, Mastro AM. The bone microenvironment in metastasis; what is special about bone? *Cancer Metastasis Rev*. 2008;27:41–55.
3. Buijs JT, van der Pluijm G. Osteotropic cancers: From primary tumor to bone. *Cancer Lett.* 2009;273:177–193.
4. Langley RR, Fidler IJ. The seed and soil hypothesis revisited – The role of tumor-stroma interactions in metastasis to different organs. *Int J Cancer*. 2011;128:2527–2535.
5. Guise T. Examining the metastatic niche: targeting the microenvironment. *Semin Oncol*. 2010;37(S2):S2–S14.
6. Logothetis C, Morris MJ, Den R, Coleman RE. Current perspectives on bone metastases in castrate-resistant prostate cancer. *Cancer Metastasis Rev*. 2018;37(1):189–196.
7. Logothetis CJ, Lin S-H. Osteoblasts in prostate cancer metastasis to bone. *Nat Rev Cancer*. 2005;5:21–28.
8. Faltermeier CM, Drake JM, Clark PM, Smith BA, Zong Y, Volpe C, Mathis C, Morrissey C, Castor B, Huang J, Witte ON. Functional screen identifies kinases driving prostate cancer visceral and bone metastasis. *Proc Natl Acad Sci U S A.* 2016;113(2):E172–E181.
9. Sathiakumar N, Delzell E, Morrisey MA, Falkson C, Yong M, Chia V, Blackburn J, Arora T, Brill I, Kilgore ML. Mortality following bone metastasis and skeletal-related events among women with breast cancer: A population-based analysis of U.S. Medicare beneficiaries, 1999-2006. *Breast Cancer Res Treat.* 2012;131:231–238.
10. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med.* 2004;360:1655–1664.
11. Keller ET, Brown J. Prostate cancer bone metastases promote both osteolytic and osteoblastic activity. *J Cell Biochem.* 2004;91:718–729.
12. Yin JJ, Mohammad KS, Käkönen SM, Harris S, Wu-Wong JR, Wessale JL, Padley RJ, Garrett IR, Chirgwin JM, Guise TA. A causal role for endothelin-1

in the pathogenesis of osteoblastic bone metastases. *Proc Natl Acad Sci U S A.* 2003;100:10954–10959.
13. Nelson JB, Nguyen SH, Wu-Wong JR, Opgenorth TJ, Dixon DB, Chung LW, Inoue N. New bone formation in an osteoblastic tumor model is increased by endothelin-1 overexpression and decreased by endothelin A receptor blockade. *Urology.* 1999;53:1063–1069.
14. Ottewell PD, Wang N, Meek J, Fowles CA, Croucher PI, Eaton CL, Holen I. Castration-induced bone loss triggers growth of disseminated prostate cancer cells in bone. *Endocr Relat Cancer.* 2014;21:769–781.
15. Dai J, Keller J, Zhang J, Lu Y, Yao Z, Keller ET. Bone morphogenetic protein-6 promotes osteoblastic prostate cancer bone metastases through a dual mechanism. *Cancer Res.* 2005;65:8274–8285.
16. Cohen P, Peehl DM, Graves HCB, Rosenfeld RG. Biological effects of prostate specific antigen as an insulin-like growth factor binding protein-3 protease. *J Endocrinol.* 1994;142:407–415.
17. Cramer SD, Chen Z, Peehl DM. Prostate specific antigen cleaves parathyroid hormone-related protein in the PTH-like domain: inactivation of PTHrP-stimulated cAMP accumulation in mouse osteoblasts. *J Urol.* 1996;156:526–531.
18. Briganti A, Suardi N, Gallina A, Abdollah F, Novara G, Ficarra V, Montorsi F. Predicting the risk of bone metastasis in prostate cancer. *Cancer Treat Rev.* 2014;40(1):3–11.
19. Hoque A, Chen H, Xu XC. Statin induces apoptosis and cell growth arrest in prostate cancer cells. *Cancer Epidemiol Biomarkers Prev.* 2008;17:88–94.
20. Zhuang L, Kim J, Adam RM, Solomon KR, Freeman MR. Cholesterol targeting alters lipid raft composition and cell survival in prostate cancer cells and xenografts. *J Clin Invest.* 2005;115:959–968.
21. Manolagas SC, O'Brien CA, Almeida M. The role of estrogen and androgen receptors in bone health and disease. *Nat Rev Endocrinol.* 2013;9:699–712.
22. Wiren KM, Evans CA, Zhang X-W. Osteoblast differentiation influences androgen and estrogen receptor-alpha and - beta expression. *J Endocrinol.* 2002;175:683–694.
23. Chiang C, Chiu M, Moore AJ, Anderson PH, Ghasem-Zadeh A, McManus JF, Ma C, Seeman E, Clemens TL, Morris HA, Zajac JD, Davey RA. Mineralization and bone resorption are regulated by the androgen receptor in male mice. *J Bone Miner Res.* 2009;24(4):621–631.
24. Russell PK, Clarke MV, Cheong K, Anderson PH, Morris HA, Wiren KM, Zajac JD, Davey RA. Androgen receptor action in osteoblasts in male mice is dependent on their stage of maturation. *J Bone Miner Res.* 2015;30:809–823.
25. Chang C, Yeh S, Lee SO, Chang TM. Androgen receptor (AR) pathophysiological roles in androgen-related diseases in skin, bone/muscle, metabolic syndrome and neuron/immune systems: lessons learned from mice lacking AR in specific cells. *Nucl Recept Signal.* 2013;11:e001.
26. Shafi AA, Yen AE, Weigel NL. Androgen receptors in hormone-dependent and castration-resistant prostate cancer. *Pharmacol Ther.* 2013;140(3):223–238.
27. Krieg M, Weisser H, Tunn S. Potential activities of androgen metabolizing enzymes in human prostate. *J Steroid Biochem Mol Biol.* 1995;53(1–6):395–400
28. Davey RA, Grossmann M. Androgen Receptor Structure, Function and Biology: From Bench to Bedside. *Clin Biochem Rev.* 2016;37(1):3–15.
29. Pihlajamaa P, Sahu B, Jänne OA. Determinants of Receptor- and Tissue-Specific Actions in Androgen Signaling. *Endocr Rev.* 2015;36(4):357–384.
30. Steers WD. 5α-reductase activity in the prostate. *Urology.* 2001;58(6 Suppl 1):17–24.
31. Dehm SM, Tindall DJ. Molecular regulation of androgen action in prostate cancer. *J Cell Biochem.* 2006;99:333–344.

32. Luo J, Attard G, Balk SP, Bevan C, Burnstein K, Cato L, Cherkasov A, De Bono JS, Dong Y, Gao AC, Gleave M, Heemers H, Kanayama M, Kittler R, Lang JM, Lee RJ, Logothetis CJ, Matusik R, Plymate S, Sawyers CL, Selth LA, Soule H, Tilley W, Weigel NL, Zoubeidi A, Dehm SM, Raj GV. Role of Androgen Receptor Variants in Prostate Cancer: Report from the 2017 Mission Androgen Receptor Variants Meeting. *Eur Urol.* 2018;73(5);715–723.
33. Cai Z, Chen W, Zhang J, Li H. Androgen receptor: what we know and what we expect in castration-resistant prostate cancer. *Int Urol Nephrol.* 2018;50(10):1753–1764.
34. Wyatt AW, Gleave ME. Targeting the adaptive molecular landscape of castration-resistant prostate cancer. *EMBO Mol Med.* 2015;7(7):878–894.
35. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, True LD, Nelson PS. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res.* 2008;68(11):4447–4454.
36. Karantanos T, Evans CP, Tombal B, Thompson TC, Montironi R, Isaacs WB. Understanding the mechanisms of androgen deprivation resistance in prostate cancer at the molecular level. *Eur Urol.* 2015;67:470–479.
37. Antonarakis ES, Armstrong AJ, Dehm SM, Luo J. Androgen receptor variant-driven prostate cancer: clinical implications and therapeutic targeting. *Prostate Cancer Prostatic Dis*. 2016;19:231–241.
38. Ho SM, Leung YK, Chung I. Estrogens and antiestrogens as etiological factors and therapeutics for prostate cancer. *Ann. N. Y. Acad. Sci.* 2006;1089:177–193.
39. Prins GS, Korach KS. The role of estrogens and estrogen receptors in normal prostate growth and disease. *Steroids.* 2008;73(3):233–244.
40. Hartman J, Ström A, Gustafsson JÅ. Current concepts and significance of estrogen receptor β in prostate cancer. *Steroids.* 2012;77:1262–1266.
41. Daniels G, Gellert LL, Melamed J, Hatcher D, Li Y, Wei J, Wang J, Lee P. Decreased expression of stromal estrogen receptor α and β in prostate cancer. *Am J Transl Res.* 2014;6:140–146.
42. Pisolato R, Lombardi APG, Vicente CM, Lucas TFG, Lazari MFM, Porto CS. Expression and regulation of the estrogen receptors in PC-3 human prostate cancer cells. *Steroids.* 2016;107:74–86.
43. Bradshaw AD. Diverse biological functions of the SPARC family of proteins. *Int. J. Biochem. Cell Biol.* 2012;44:480–488.
44. Murphy-Ullrich JE, Sage EH. Revisiting the matricellular concept. *Matrix Biol.* 2014;37:1–14.
45. Rosset EM, Bradshaw AD. SPARC/Osteonectin in Mineralized Tissue. *Matrix Biol.* 2016;52–54:78–87.
46. Kelm RJ Jr, Mann KG. The collagen binding specificity of bone and platelet osteonectin is related to differences in glycosylation. *J. Biol. Chem.* 1991;266:9632–9639.
47. Termine JD, Kleinman HK, Whitson SW, Conn KM, McGarvey ML, Martin GR. Osteonectin, a bone-specific protein linking mineral to collagen. *Cell.* 1981;26:99–105.
48. Delany AM, Hankenson KD. Thrombospondin-2 and SPARC/osteonectin are critical regulators of bone remodeling. *J. Cell Commun. Signal.* 2009;3:227–238.
49. Trombetta JM, Bradshaw AD. SPARC/Osteonectin Functions to Maintain Homeostasis of the Collagenous Extracellular Matrix in the Periodontal Ligament. *J Histochem Cytochem.* 2010;58(10):871–879.
50. Ingber D, Folkman J. Mechanochemical switching between growth and differentiation during fibroblast growth factor-stimulated angiogenesis in vitro: role of extracellular matrix. *J Cell Biol.* 1989;109:317–330.
51. Thomas R, True LD, Bassuk JA, Lange PH, Vessella RL. Differential expression of osteonectin/SPARC during human prostate cancer progression. *Clin Cancer Res.* 2000;6(3):1140–1149.

52. Brekken RA, Sage EH. SPARC, a matricellular protein: at the crossroads of cell-matrix communication. *Matrix Biol.* 2001;19:816–827.
53. Breton-Gorius J, Clezardin P, Guichard J, Debili N, Malaval L, Vainchenker W, Cramer EM, Delmas PD. Localization of platelet osteonectin at the internal face of the alpha-granule membranes in platelets and megakaryocytes. *Blood.* 1992;79:936–941.
54. Reed MJ, Puolakkainen P, Lane TF, Dickerson D, Bornstein P, Sage EH. Differential expression of SPARC and thrombospondin 1 in wound repair: immunolocalization and in situ hybridization. *J. Histochem. Cytochem.* 1993;41:1467–1477.
55. Sage H, Johnson C, Bornstein P. Characterization of a novel serum albuminbinding glycoprotein secreted by endothelial cells in culture. *J Biol Chem.* 1984;259:3993–4007.
56. McCabe NP, Kerr BA, Madajka M, Vasanji A, Byzova TV. Augmented Osteolysis in SPARC-Deficient Mice with Bone-Residing Prostate Cancer. *Neoplasia.* 2011;13(1):31–39.
57. Ruela-Arispe M L, Lane T F, Redmond D, Reilly M, Bolender RP, Kavanagh TJ, Sage EH. Expression of SPARC during development of the chicken chorioallantoic membrane: evidence for regulated proteolysis in vivo. *Mol. Biol. Cell.* 1995;6: 327–343.
58. Burns-Cox N, Avery NC, Gingell JC, Bailey AJ. Changes in collagen metabolism in prostate cancer: a host response that may alter progression. *J Urol.* 2001;166(5):1698–1701.
59. Gao J, Song J, Huang H, Li Z, Du Y, Cao J, Li M, Lv S, Lin H, Gong Y. Methylation of the SPARC gene promoter and its clinical implication in pancreatic cancer. *J Exp Clin Cancer Res.* 2010;29(1):28.
60. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: regulators of the tumor microenvironment. *Cell.* 2010;141:52–67.
61. Hynes RO, Naba A. Overview of the matrisome – an inventory of extracellular matrix constituents and functions. *Cold Spring Harb Perspect Biol.* 2012;4(1):a004903.
62. Cierna Z, Mego M, Janega P, Karaba M, Minarik G, Benca J, Sedlácková T, Cingelova S, Gronesova P, Manasova D, Pindak D, Sufliarsky J, Danihel L, Reuben JM, Mardiak J. Matrix metalloproteinase 1 and circulating tumor cells in early breast cancer. *BMC Cancer*. 2014;14:472.
63. Mohan V, Talmi-Frank D, Arkadash V, Papo N, Sagi I. Matrix metalloproteinase protein inhibitors: highlighting a new beginning for metalloproteinases in medicine. *Metalloproteinases in medicine.* 2016;3:31–47.
64. Radisky ES, Radisky DC. Matrix metalloproteinase-induced epithelial-mesenchymal transition in breast cancer. *J Mammary Gland Biol Neoplasia.* 2010;15:201–212.
65. Mannello F. What does matrix metalloproteinase-1 expression in patients with breast cancer really tell us? *BMC Med.* 2011;9:95.
66. Hu F, Zhang Y, Li M, Zhao L, Chen J, Yang S, Zhang X. BMP-6 inhibits the metastasis of MDA-MB-231 breast cancer cells by regulating MMP-1 expression. *Oncol. Rep.* 2016;35:1823–1830.
67. Liu M, Hu Y, Zhang M-F, Luo K-J, Xie X-Y, Wen J, Fu JH, Yang H. MMP1 promotes tumor growth and metastasis in esophageal squamous cell carcinoma. *Cancer Letters.* 2016;377(1):97–104.
68. Lu X, Wang Q, Hu G, Van Poznak C, Fleisher M, Reiss M, Massagué J, Kang Y. ADAMTS1 and MMP1 proteolytically engage EGF-like ligands in an osteolytic signaling cascade for bone metastasis. *Genes Dev.* 2009;23:1882–1894
69. Casimiro S, Mohammad KS, Pires R, Tato-Costa J, Alho I, Teixeira R, Carvalho A, Ribeiro S, Lipton A, Guise TA, Costa L. RANKL/RANK/MMP-1 Molecular Triad Contributes to the Metastatic Phenotype of Breast and Prostate Cancer Cells In Vitro. *PLoS One.* 2013;8(5):e63153.
70. Ozden F, Saygin C, Uzunaslan D, Onal B, Durak H, Aki H. Expression of MMP-

1, MMP-9 and TIMP-2 in prostate carcinoma and their influence on prognosis and survival. *J. Cancer Res. Clin. Oncol.* 2013;39:1373–1382.

71. Bianchi ME. Damps, pamps and alarmins: all we need to know about danger. *J. Leukoc. Biol.* 2007;81:1–5.
72. Min HJ, Choe JW, Chang MY, Kim KS, Lee SY, Mun SK. The expression and correlation of Hsp 70 and Hsp 27 in serous middle ear effusion fluids of pediatric patients-a preliminary study. *International Journal of Pediatric Otorhinolaryngology*. 2017;101:145–149.
73. Wu J, Liu T, Rios Z, Mei Q, Lin X, Cao S. Heat Shock Proteins and Cancer. *Trends Pharmacol. Sci.* 2017;38:226–256.
74. Gabai VL, Budagova KR, Sherman MY. Increased expression of the major heat shock protein Hsp72 in human prostate carcinoma cells is dispensable for their viability but confers resistance to a variety of anticancer agents. *Oncogene.* 2005;24:3328.
75. Jindal DG, Jindal V, Joshi S, Bhojia I, Chawdhr A. Heat shock proteins in pathology: A review. *Journal of Pierre Fauchard Academy (India Section).* 2016;30(3–4):84–87.
76. Helmbrecht K, Zeise E, Rensing L. Chaperons in cell cycle regulation and mitogenic signal transduction: a review. *Cell Prolif.* 2000;92:1564.
77. Ni L, Yang CS, Gioeli D, Frierson H, Toft DO, Paschal BM. FKBP51 Promotes Assembly of the Hsp90 Chaperone Complex and Regulates Androgen Receptor Signaling in Prostate Cancer Cells. *Mol Cell Biol.* 2010;30(5):1243–1253.
78. Heinlein CA, Chang CS. Androgen receptor in prostate cancer. *Endocr. Rev.* 2004;25:276–308.
79. Kurahashi T, Miyake H, Hara I, Fujisawa M. Expression of Major Heat Shock Proteins in Prostate Cancer: Correlation With Clinicopathological Outcomes in Patients Undergoing Radical Prostatectomy. *The Journal of Urology*. 2007;177(2):757–761.
80. Narula S, Tandon S, Baligar P, Singh SK, Tandon C. Human kidney stone matrix: Latent potential to restrain COM induced cytotoxicity and inflammatory response. *Chemico-Biological Interactions.* 2017; 278:114–122.
81. Melman A. *Synthesis of Inorganic Nanoparticles Using Protein Templates. Fine Particles in Medicine and Pharmacy*. New York: Springer US, 2012, 340 p.
82. Chen E, Xue D, Zhang W, Lin F, Pan Z. Extracellular heat shock protein 70 promotes osteogenesis of human mesenchymal stem cells through activation of the ERK signaling pathway. *FEBS Letters.* 2015;589(24, parn B):4088–4096.
83. Fong-Ngern K, Sueksakit K, Thongboonkerd V. Surface heat shock protein 90 serves as a potential receptor for calcium oxalate crystal on apical membrane of renal tubular epithelial cells. *J Biol Inorg Chem.* 2016;21(4):463–74.
84. Li K, Xue Y, Chen A, Jiang Y, Xie H, Shi Q, Zhang S, Ni Y. Heat Shock Protein 90 Has Roles in Intracellular Calcium Homeostasis, Protein Tyrosine Phosphorylation Regulation, and Progesterone-Responsive Sperm Function in Human Sperm. *PLoS One.* 2014;9(12):e115841.
85. Kato K, Adachi S, Matsushima-Nishiwaki R, Minamitani C, Natsume H, Katagiri Y, Hirose Y, Mizutani J, Tokuda H, Kozawa O, Otsuka T. Regulation by Heat Shock Protein 27 of Osteocalcin Synthesis in Osteoblasts. *Endocrinology*. 2011;152(5):1872–1882.
86. Spierings D, McStay G, Saleh M, Bender C, Chipuk J, Maurer U, Green DR. Connected to death: the (unexpurgated) mitochondrial pathway of apoptosis. *Science*. 2005;310(5745):66–67.
87. Wajant H. The Fas signaling pathway: more than a paradigm. *Science*. 2002;296(5573):1635–1636.
88. Adams JM, Cory S. The Bcl-2 apoptotic switch in cancer development and therapy. *Oncogene.* 2007;26(9):1324–1337.

89. Hu J, Duan Z, Yu G, Wang S. Bcl-2 Inhibitors as Sensitizing Agents for Cancer Chemotherapy. *Protein Kinase Inhibitors as Sensitizing Agents for Chemotherapy*. 2019:151–168.
90. Green DR, Kroemer G. Cytoplasmic functions of the tumour suppressor p53. *Nature.* 2009;458:1127–1130.
91. Thornton C, Hagberg H. *Fetal and Neonatal Physiology (Fifth Edition).* London: Elsevier, 2017, 1928 p.
92. Chappell WH, Lehmann BD, Terrian DM, Abrams SL, Steelman LS, McCubrey JA. p53 expression controls prostate cancer sensitivity to chemotherapy and the MDM2 inhibitor Nutlin-3. *Cell Cycle.* 2012;11(24):4579–4588.
93. Oren M, Rotter V. Mutant p53 gain-of-function in cancer. *Cold Spring Harb Perspect Biol.* 2010;2:a001107.
94. Chang YJ, Linh NH, Shih YH, Yu HM, Li MS, Chen YR. Alzheimer's amyloid-beta sequesters caspase-3 in vitro via its C-terminal tail. *ACS Chem Neurosci.* 2016;7:1097–1106.
95. Flanagan L, Meyer M, Fay J, Curry S, Bacon O, Duessmann H, John K, Boland KC, McNamara DA, Kay EW, Bantel H, Schulze-Bergkamen H, Prehn JH. Low levels of caspase-3 predict favourable response to 5FU-based chemotherapy in advanced colorectal cancer: caspase-3 inhibition as a therapeutic approach. *Cell Death Dis.* 2016;7:e2087.
96. Rodríguez-Berriguete G, Galvis L, Fraile B, de Bethencourt FR, Martínez-Onsurbe P, Olmedilla G, Paniagua R, Royuela M. Immunoreactivity to caspase-3, caspase-7, caspase-8, and caspase-9 forms is frequently lost in human prostate tumors. *Human Pathology.* 2012;43:229–237.
97. Ashkenazi A, Salvesen G. Regulated Cell Death: Signaling and Mechanisms. *Annual Review of Cell and Developmental Biology.* 2014;30:337–356.
98. Bleicken S, Landeta O, Landajuela A, Basanez G, García-Saez AJ. Proapoptotic Bax and Bak Proteins Form Stable Protein-permeable Pores of Tunable Size. *The journal of biological chemistry.* 2013;288(46):33241–33252.
99. Rostamzadeh A, Ghadimi T, Allahveisi A, Mohammadi M, Rezaei S, Rezaie MJ. The expression of Bax protein in the early stages of spinal cord injury in the sperm cells of rats. *Polish Annals of Medicine.* 2018;25(2):196–202.
100. Snigdha S, Smith ED, Prieto GA, Cotman CW. Caspase-3 activation as a bifurcation point between plasticity and cell death. *Neuroscience Bulletin.* 2012;28(1):14–24.
101. Hernández-Luna MA, Díaz de León-Ortega R, Hernández-Cueto DD, Gaxiola-Centeno R, Castro-Luna R, Martínez-Cristóbal L, Huerta-Yépez S, Luria-Pérez R. Bactofection of sequences encoding a Bax protein peptide chemosensitizes prostate cancer tumor cells. *Bol Med Hosp Infant Mex.* 2016;73(6):388–396.
102. Maji S, Panda S, Samal S K, Shriwas O, Rath R, Pellecchia M, Emdad L, Das SK, Fisher PB, Dash R. Bcl-2 Antiapoptotic Family Proteins and Chemoresistance in Cancer. *Advances in Cancer Research.* 2018;137:37–75.
103. Westphal D, Kluck RM, Dewson G. Building blocks of the apoptotic pore: how Bax and Bak are activated and oligomerize during apoptosis. *Cell Death & Differentiation.* 2014;21(2):196–205.
104. Yuan Z, Jiang H, Zhu X, Liu X, Li L. Ginsenoside Rg3 promotes cytotoxicity of Paclitaxel through inhibiting NF-κB signaling and regulating Bax/Bcl-2 expression on triple-negative breast cancer. *Biomedicine & Pharmacotherapy.* 2017;89:227–232.
105. Kervancioglu E, Kosan M, Erinanc H, Gonulalan U, Oguzulgen AI, Coskun EZ, Ozkardes H. Predictive values of vascular endothelial growth factor and microvessel-density levels in initial biopsy for prostate cancer. *The Kaohsiung Journal of Medical Sciences.* 2016;32(2):74–79.
106. Liu ZQ, Fang JM, Xiao YY, Zhao Y, Cui R, Hu F, Xu Q. Prognostic role of vascular endothelial growth factor in prostate cancer: A systematic review and meta-analysis. *Int J Clin Exp Med.* 2015;8:2289–2298.

107. Nordby Y, Andersen S, Richardsen E, Ness N, Al-Saad S, Melbø-Jørgensen C, Patel HR, Dønnem T, Busund LT, Bremnes RM. Stromal expression of VEGF-A and VEGFR-2 in prostate tissue is associated with biochemical and clinical recurrence after radical prostatectomy. *Prostate.* 2015;75:1682–1693.
108. Rivera-Pérez J, Monter-Vera MDR, Barrientos-Alvarado C, Toscano-Garibay JD, Cuesta-Mejías T, Flores-Estrada J. Evaluation of VEGF and PEDF in prostate cancer: A preliminary study in serum and biopsies. *Oncology Letters.* 2018;15:1072–1078.
109. Djordjevic S, Driscoll PC. Targeting VEGF signalling via the neuropilin co-receptor. *Drug Discov. Today.* 2013;18:447–455.
110. Shibuya. M. VEGF-VEGFR signals in health and disease. *Biomol Ther.* 2014;22:1–9.
111. Roberts E, Cossigny DAF, Quan GMY. The Role of Vascular Endothelial Growth Factor in Metastatic Prostate Cancer to the Skeleton. *Prostate Cancer.* 2013:418340.
112. Gerber H-P, Vu TH, Ryan AM, Kowalski J, Werb Z, Ferrara N. VEGF couples hypertrophic cartilage remodeling, ossifcation and angiogenesis during endochondral bone formation. *Nature Medicine.* 1999;5(6):623–628.
113. Cossigny D, Quan GMY. In vivo animal models of spinal metastasis. *Cancer and Metastasis Reviews.* 2012;31(1):99–108.
114. Curtin P, Youm H, Salih E. Tree-dimensional cancerbone metastasis model using ex-vivo co-cultures of live calvarial bones and cancer cells. *Biomaterials.* 2012;33(4):1065–1078.
115. Karan D, Dubey S. From Inflammation to Prostate Cancer: The Role of Inflammasomes. *Adv Urol.* 2016;2016:3140372.
116. Coussens LM, Werb Z. Inflammation and cancer. *Nature.* 2002;420:860–867.
117. Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell.* 2009;139:871–890.
118. Zhu XD, Zhang JB, Zhuang PY, Zhu HG, Zhang W, Xiong YQ, Wu WZ, Wang L, Tang ZY, Sun HC. High expression of macrophage colony-stimulating factor in peritumoral liver tissue is associated with poor survival after curative resection of hepatocellular carcinoma. *J Clin Oncol.* 2008;26:2707–2716.
119. Steidl C, Lee T, Shah SP, Farinha P, Han G, Nayar T, Delaney A, Jones SJ, Iqbal J, Weisenburger DD, Bast MA, Rosenwald A, Muller-Hermelink HK, Rimsza LM, Campo E, Delabie J, Braziel RM, Cook JR, Tubbs RR, Jaffe ES, Lenz G, Connors JM, Staudt LM, Chan WC, Gascoyne RD. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. *N Engl J Med.* 2010;362:875–885.
120. Wu Y, Deng J, Rychahou PG, Qiu S, Evers BM, Zhou BP. Stabilization of snail by NF-kappaB is required for inflammation-induced cell migration and invasion. *Cancer Cell.* 2009;15:416–428.
121. Hoesel B, Schmid JA. The complexity of NF-κB signaling in inflammation and cancer. *Molecular Cancer.* 2013;12(1);86.
122. Mishra A, Shiozawa Y, Pienta KJ, Taichman RS. Homing of cancer cells to the bone. *Cancer Microenviron.* 2011,4:221–235.
123. Scimeca M, Urbano N, Rita B, Mapelli SN, Catapano CV, Carbone GM, Ciuffa S, Tavolozza M, Schillaci O, Mauriello A, Bonanno E. Prostate Osteoblast-Like Cells: A Reliable Prognostic Marker of Bone Metastasis in Prostate Cancer Patients. *Contrast Media Mol Imaging.* 2018;2018:9840962.

(received 23.05.2019, published online 26.06.2019)

(одержано 23.05.2019, опубліковано 26.06.2019)