Review Article

The role of NF-KB and estrogen receptor on prostate cancer progression to bone metastasis

Review

Prostate cancer is the sixth highest cause of mortality in men world-wide.[1] Some patients die suddenly, while others experience a rapid development to a life threatening disease.[1] The year 2015 recorded 27, 540 prostate cancer (PCa) deaths,[2] possibly as result of bone metastasis. The skeleton is known for metastatic activities and bone break down is the primary cause of cancer death. The occurrence of bone metastases makes the initial cancer incurable.[3]

Inflammation in general and NF-κB specifically have a multiple action in cancer. NF-κB activities attack and eliminate neoplasia cells. Complete activation of NF-κB is followed by a high reaction of immune cells fighting against transformed cells.[4] NF-κB cross talk controls numerous life supporting mechanisms, such as cell proliferation[5] and apoptosis.[5]

NF-κB was first known as a transcription factor in 1986. It was described as a nuclear factor attached to the DNA of the immunoglobulin kappa light-chain of activated B cells.[6] Consequently, proteins which possess this special DNA binding activity are functional in most cell types and control many related genes with numerous functions.[7]

Numerically, five divisions of transcription factor family have been classified. These are tagged as p65 (RelA), RelB, c-Rel, NF-κB1 and NF-κB2. In dissimilarity to the other family divisions, NF-κB1 and NF-κB2 are produced in inactive forms (p105 and p100) and are enzymatically broken down to the active forms (p50 and p52), respectively.[8] All the five divisions of this protein family tree form homo- or heterodimers and have similar structural features. They have Rel homology domain (RHD). RHD is important for combination, as well as linking to associate DNA elements.[9] NF-κB sub units consist of regions for phosphorylations and other after-translational alterations. These regions are necessary for activation and signal transduction link with other signaling pathways.[10] Attachment of NF-κB dimers to IκB molecules hinder binding to DNA, and shift the balance-state localization of the complex to the cytoplasm. In spite of that, movement between cytoplasm and nucleus takes place.[11]

Numerous activation processes ensure that various stress circumstances can initiate the enzymatic activities of IKKs. These cause the bio-availability of the general stress response factor NF-κB. Furthermore, they provide a basis for complex signal transduction with other signaling pathways. It is likely that many of the feedback inhibitors are de-ubiquitinases (DUB's) such as A20[7] or CYLD.[12]

Bone metastasis occurs often in the fourth stage of prostate cancer. This leads to serious diseases including pain, disease causing broken bone, spinal cord deformity, and disability. Systemic androgen deprivation is effective in controlling metastasis. However, the metastatic mass eventually become resistant to hormonal or chemotherapeutic treatment and continue to multiply.[13]

Bone metastases may lead to osteolytic, osteosclerotic, or mixed lesions. Osteolytic metastases occur as a result of increased action of bone-breaking cells, the osteoclasts (OCs). OCs damages the bone.[14] About 65-75% of prostate cancer patients experience bone metastases during the development of cancer.[15]

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The NF-κB pathway is also a key mediator of genes responsible for cellular proliferation and apoptosis.[16] The inhibition of NF-κB trans activation may be part of a negative feedback loop that contributes to resolution of inflammation and cancer.[16]

Osteoprotegerin (OPG) is a decoy receptor for Receptor Activator of Nuclear Factor Kappa-B ligand (RANKL). OPG binds to RANKL, this leads to reduced production of osteoclasts by inhibiting the maturation of osteoclast precursors. Bone resorption/remodeling are a complex process regulated by a large variety of molecules.[17] The RANKL to OPG magnitude is the key regulatory determinant of bone resorption. Bone resorption is favored by high RANKL to OPG ratio.[17] Genistein (10 mg/kg, in subcutaneous administration) significantly increased serum OPG level as well as decreased serum RANKL level and the RANKL/OPG ratio in ovariectomized rats.[18] Therefore, impacting apoptosis induction through NF-KB inhibition.

The effect of vitamin C on NF-κB in vitro suggests concentration dependent; one study indicated that 0.2 mM ascorbate enhanced NF-κB activation in Jurkat T-cells,[19] while two other studies using higher ascorbate concentrations showed inhibition of NF-κB in endothelial cells[20] and other human cell types. Combination treatment of genistein and vitamin C permits more LNCaP prostate cancer cells to live than the single treatment of genistein in vitro, although there was more apoptosis in the combination treatment of genistein and vitamin C.[21] Future studies should evaluate a possible synergy between the combination treatment (genistein and vitamin C treatment) and NF-KB pathway inhibition.

Studies have characterized the constituent of exosomes liberated by the metastatic prostate cancer cell line PC-3 at the polypeptide,[21] lipid[23] and micro RNA step.[24] It has been suggested that inhibition of V-ATPase impacts prostate cancer invasion and PSA level.[25,26] In the same vein, down-regulation of LASS2/TMSG1 (which decreases V-ATPase activity through V0c-attachment) led to greater metastasis and prostate cancer growth.[27] Exosomes are one of the tumor derived factors inducing vascular leakiness, inflammation and bone marrow progenitor cell recruitment during pre-metastatic niche formation and metastasis.[28]

Surprisingly, bone-tropic exosomes expressed a limited integrin store, but were capable of inducing vascular leakiness in the lung. Although, induction of vascular leakiness may be the first exosome-mediated step during the metastatic cascade, it is insufficient to promote bonemetastasis. Integrin-dependent mechanisms may not mediate vascular leakiness and exosome activity in bone metastasis.[29]

In kB site-dependent reporter gene assays, ER-alpha has been shown to down regulate NF-kB activity in an estrogen-dependent mechanism at Nano molar concentrations of estrogen. This occurs in many cell lines, such as U2-OS,[30] F9,[31] HeLa,[32,33] 293,[34] U937,[35] HepG2[36] and MCF-7[37] cells. Many groups have also shown that ER-b has an inhibitory effect on NF-kB activity.[32–39]

The cross-talk between these transcription factors suggests relevance to bone physiology, inflammation, cancer and autoimmune diseases. However, the process of down-regulation of NF-kB by ER is manifold and may be specific to cell type and context. Many essential technical questions remain unanswered about the signal transduction between the ER and NF-kB. What is the extent of the inhibition of NF-kB target genes by ER-alpha? What percentage of NF-kB target genes is inhibited by ER-alpha? Studies have shown that ER-alpha can selectively inhibit NF-kB target genes; ER-alpha inhibits NF-kB-mediated transcriptional induction of the IL-6 gene in almost all cancer types, but not that of the TRAF1 (Tumor necrosis factor receptor-associated factor 1) gene in the MDA-MB-231 breast cancer cell line.[40] Are there particular SERMs (Selective Estrogen Receptor Modulators) that enhance the ability of the ER to repress NF-kB activity? And can these SERMs be used to counter NF-kB activity in some diseases? Does the ER exert its anti- or pro-apoptotic effects through modulation of NF-kB? Finding the solutions to these questions will supply a beneficial need for further research.

Conclusion

In summary, NF-kB induced expression of the gene encoding IL-6. This contributes to breaking down of bone tissue.[41] Members of the NF-kB family function to promote bone resorption through the regulation of cytokines such as interleukein-6 (IL-6)[41] and estrogen acts to inhibit this process.[42] Furthermore, the anti-inflammatory roles of the ER in many animal models of disease and human disorders[42–44] might be explained by inhibition of the pro-inflammatory activities of NF-kB.[45]

RANKL is an important factor for osteoclastogenesis because it stimulates maturation of myeloid precursor cells into osteoclasts by binding to its signaling receptor.[46] RANKL expression was shown to be induced by IL-6/ sIL-6R but not IL-6 alone via the JAK/STAT signaling pathway.[46] Appropriately, neutralizing anti-IL-6mAbs inhibited osteoclast production. IL-6 levels and some IL-6 gene polymorphisms have been associated with bone mineral density alterations in inflammatory disease.[47] IL-6 plays an important role in the regulation of bone metastasis, presumably via IL-6 trans-signaling.

The NF-kB group of transcription factors direct numerous aspects of the immune and skeletal systems' inflammatory responses. Chronic NF-kB activity has been implicated in various diseases including arthritis, diabetes, atherosclerosis, Alzheimer's disease and several cancers.[48,49] Future studies should evaluate a possible synergy between the combination treatment (genistein and vitamin C treatment) and NF-KB pathway inhibition. Concerted research effort should be on studying integrin-independent mechanisms mediating vascular leakiness and exosome involvement in bone metastasis.

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