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Review article

P62: An emerging oncotarget for osteolytic metastasis

Jing Zhang [a], Zuozhang Yang [a], Jian Dong [a,b,*]

[a] Bone and Soft Tissue Tumors Research Center of Yunnan Province, Department of Orthopaedics, The Third Affiliated Hospital of Kunming Medical University, Tumor Hospital of Yunnan Province, Kunming, Yunnan 650118, PR China
[b] Stem Cell Therapy Technical of Clinical Transformation and Basic Research Key Laboratory of Yunnan Province, Kunming, Yunnan 650118, PR China

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ABSTRACT

Bone metastasis occurs in the majority of late-stage tumors with poor prognosis. It is mainly classified as osteoblastic metastasis and osteolytic metastasis. The pathogenesis of osteolytic metastasis is a "vicious cycle" between tumor cells and bone cells (primarily the osteoclasts), which is mediated by secretory factors. The P62 adapter protein is a versatile multitasker between tumor cells and bone cells. The overexpression of P62 has been detected among a variety of tumors, playing positive roles in both tumorigenesis and metastasis. Moreover, P62 is an important modulator of the osteoclastogenesis pathway. Therefore, the ability of P62 to modulate tumors and osteoclasts suggests that it may be a feasible oncotarget for bone metastasis, especially for osteolytic metastasis. Recent research has shown that a P62 DNA vaccine triggered effective anti-tumor, anti-metastatic and anti-osteoporotic activities. Growing lines of evidence point to P62 as an emerging oncotarget for osteolytic metastasis. In this review, we outline the different roles of P62 in tumor cells and osteoclasts, focusing on the P62-related signaling pathway in key steps of osteolytic metastasis, including tumorigenesis, metastasis and osteoclastogenesis. Finally, we discuss the newest observations on P62 as an oncotarget for osteolytic metastasis treatment.

Contents

1. Introduction

Up to 90% of patients with multiple myeloma, and 60–75% patients with prostate cancer and breast cancer develop bone metastasis at the later stages of their diseases [1]. Metastatic

* Corresponding author at: Bone and Soft Tissue Tumors Research Center of Yunnan Province, Department of Orthopaedics, The Third Affiliated Hospital of Kunming Medical University, Tumor Hospital of Yunnan Province, Kunming, Yunnan 650118, PR China.
E-mail address: nmlimit@sina.com (J. Dong).

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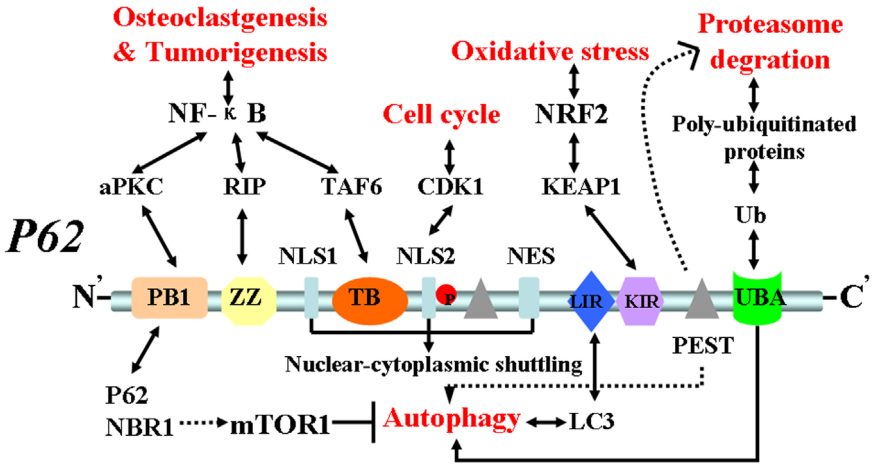

Fig. 1. *P62 structure, interaction domains and function.* P62 has six main functional domains: PB1, ZZ, TB, LIR, KIR and UBA. The PB1 domain binds PKC. The ZZ zinc-finger domain binds receptor interacting protein (RIP).The TRAF6 binding (TB) domain binds TRAF6. Three domains link p62 to NF-κB activation, which is relevant in RANK-induced osteoclastogenesis, as well as in Ras-induced tumorigenesis. PB1 domain also self- and hetero- oligomerizes with NBR1, which might restrain autophagy through mTOR activation. The LIR domain interacts with autophagosome protein LC3, serving to control p62 levels in autophagy. The KIR domain binds Keap1, which might be important for the regulation of Nrf2 and the control of ROS levels in oxidative stress. The UBA domain regulates the interaction of p62 with poly-ubiquitylated proteins targeted for degradation by the proteasome or autophagy. In addition, p62 has two PEST sequences that are targets for post-translation modifications and degradation. P62 also contains two NLS sequences and a NES sequence which allow p62 shuttling into and out of nucleus. NLS2 domain phosphorylated by CDK1 that regulates cell cycle.

lesions in bone are significantly associated with bone pain, hypercalcemia or hypocalcemia, pathological fracture and spinal cord compression, which mostly correlated to low 5-years survival-rate less than 30% [2]. Relative to osteoblastic metastasis, osteolytic metastasis is more difficult to treat, making the need to study its pathogenesis. Recent advances in the understanding of osteolytic metastasis revealed that it is associated with characteristic modulations of the bone microenvironment and cross-talk between the tumor cells and bone cells (primarily the osteoclasts). Tumor cells condition the “metastatic niche” through the secretion of soluble factors that stimulate bone resorption by the osteoclasts. Osteoclastic bone resorption results in the release and activation of growth factors in the bone microenvironment that further stimulate tumor growth, leading to a “vicious cycle” [3]. It is involved with numerous signaling factors, but the crucial molecules are still uncertain [1].

Since its initial discovery as an atypical protein kinase C (PKC)-interacting protein, P62 (also known as sequestosome-1, SQSTM-1 or A170) has emerged as a crucial molecule in the regulation of cell growth, survival and proliferation [4]. The human P62 protein has 440 amino acid residues and contains different types of protein–protein interaction domains. The multi-functional domains of the P62 adapter protein are consistent with its role as a versatile multitasker in signal transduction in tumors [5], (Fig. 1). P62 accumulation promotes tumorigenesis [6]. It is found to be either not expressed or found at low levels of expression in normal tissues, but is over-expressed among various types of tumors and, for the most part, is correlated with tumor migration, invasion or metastasis [7–24]. Thus, the P62 gene is generally acknowledged to be an oncogene. In addition, many studies on Paget's disease of bone (PDB), which is a skeletal disorder characterized by osteolytic lesions and overactive osteoclasts, have identified P62 as an important modulator of the osteoclastogenesis pathway [25–27]. The dysregulated expression of the P62 protein promotes osteoclastogenesis, bone resorption and osteolytic lesions. Therefore, P62 has long been thought of as a promising molecular target in PDB and other bone metabolic diseases [28].

Many *in vitro* and *in vivo* studies employing knockdown have shown that P62 can inhibit tumor formation, proliferation and/or progression [29–31]. Recent research on intramuscularly or intravenously administered P62 DNA vaccines showed that they induced anti-P62 antibodies and exhibited strong anti-tumor and anti-metastatic activities in transplantable mouse tumors [32] and canine spontaneous mammary neoplasm models [33]. The latest research reported the unexpected finding that intramuscular delivery of P62 DNA vaccines exerts a powerful anti-osteoporotic activity in a mouse model of inflammatory bone loss [34]. These studies promoted P62 as an oncotarget for bone metastasis, especially for osteolytic metastasis.

In this review, we outline the different role of P62 in tumor cell and osteoclast, focusing on the P62-related signal pathway in key steps of osteolytic metastasis, including tumorigenesis, metastasis and osteoclastogensis. Finally, we discuss the newest observations about P62 as an oncotarget for osteolytic metastasis treatment.

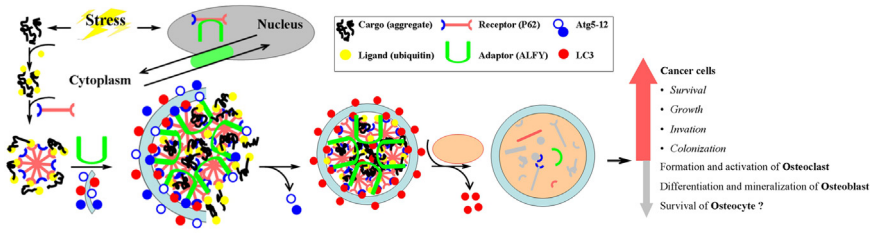

Fig. 2. *Receptor P62 in aggrephagy model.* The ligand (ubiquitin) is the recognition component on the cargo (aggregate-prone proteins) that binds a receptor (P62). The interaction between the receptor and adapter is vital for cargo recruitment to the phapophore assembly site, where an autophagosome forms. Adapter autophagy-linked FYVE protein (ALFY) interacts both with the receptor P62 and with components of the core Atg5–Atg12 machinery to facilitate formation of the autophagosomal membrane around the cargo to be degraded.