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Mini-review

Osteopontin and their roles in hematological malignancies: Splice variants on the new avenues

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ABSTRACT

Osteopontin (OPN) is a protein expressed in several tissues, including bone marrow, in which it performs distinct roles, such as modulating hematopoietic stem cell niche and bone remodeling. Most data in hematological malignancies (HMs) refers to total OPN (tOPN), comprehending the sum of distinct OPN splicing isoforms (OPN-SI), while reports describing the expression and roles of each OPN-SI are scarce. This review aims to summarize tOPN roles in HMs and provide evidence that OPN-SIs can also modulate specific functions in HMs biology. We summarize that upregulated tOPN can modulate HMs (leukemia, lymphoma and myeloma) progression, inducing cell adhesion, invasion, angiogenesis, cell differentiation and extramedullary and/or central nervous system infiltration. Based on this expression pattern, tOPN has been pointed out as a biomarker in those HMs, thus providing potential targets for therapeutic approaches. Our group found that OPN-SIs are expressed in childhood B-cell precursor acute lymphoblastic leukemia (BCP-ALL) cell lines (unpublished data), providing early evidence that OPN-SIs are also expressed in BCP-ALL. Further studies should investigate whether these OPN-SIs can differently modulate HMs biology and their putative application as auxiliary biomarkers for HMs.

Introduction

Among several proteins overexpressed in cancer, osteopontin (OPN) has been largely investigated in several cancer types, including hematologic malignancies (HMs) [1–3]. OPN is a non-collagenus matrix protein produced by various cells, including osteoblasts, osteoclasts and several types of malignant and non-malignant cells [4]. In solid tumors, the roles of OPN on modulating several steps in tumor progression is well established [1]. In these tumors, OPN expression has been clearly correlated to cell proliferation, migration, invasion and metastatic potential [1,5,6]. Also, OPN expression has been broadly suggested as a tumor biomarker [7]. However, OPN functions in HMs, particularly in early disease development and cell differentiation, are still under investigation. In HMs, although generally overexpressed, OPN exhibits distinct expression patterns, depending on the hematopoietic cell lineage involved, either lymphoid or myeloid. In this regard, OPN roles as additional diagnostic and prognostic marker are yet to be determined and controversial findings have been reported so far [3,6]. Despite the knowledge of OPN wide overexpression in HMs, its roles on modulating tumor cell differentiation and on controlling the bone marrow (BM) niche remain to be further investigated. Besides total OPN (tOPN), which is the main focus of most studies of OPN in cancer, the roles of each OPN splicing isoform (OPN-SI) in solid tumors have been investigated in several tumor types [8,9]. Conversely, OPN-SI expression and contributions in distinct biological and prognostic aspects of HM is starting to be investigated [10]. In this context, the current review aims to discuss known OPN roles on HMs, particularly leukemias, lymphomas and myelomas. Herein, we also highlight tOPN levels as putative HM biomarkers and their roles on modulating hematopoiesis and stem cell properties into the BM niche. Moreover, we also discuss putative tOPN contributions on infiltrating extramedullary sites, including central nervous system (CNS) invasion. Further, our group provides herein early evidence that similarly to solid tumors, OPN-SIs are also expressed in HMs, as demonstrated in acute leukemia cells.

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OPN: features, protein structure and isoforms

OPN, also known as early T-cell activation gene-1, SPP1 or ETA-1, is a matricellular, mainly secreted, multifunctional glycophosphoprotein. OPN exhibits either a full-length molecule or proteolytic fragments and transcriptionally processed variants. Intracellular OPN expression has also been described [11–13]. Multiple post-translation isoforms of OPN have been reported, including several glycosylated, phosphorylated, sulfated, and non-sulfated species [14,15]. The sum of these variants comprehends tOPN, which is the main focus of investigations regarding physiopathological roles of OPN. OPN is subject to genetic variation, and variants of the OPN gene, such as those exhibiting single-nucleotide polymorphisms (SNPs) and alternative splicing, could contribute to the development and/or progression of specific cancers [5]. Upon alternative splicing, OPN primary transcript produces at least 3 main OPN-SI, named OPNa, OPNb and OPNc. OPNa is the full length isoform, while OPNb and OPNc lack exons 5 and 4, respectively [8]. More recently, two additional OPN-SI have been reported, named isoform 4 (OPN4) and isoform 5 (OPN5), which sequences are deposited in NCBI, ENA and UniProt repositories. OPN4, also known as the transcript variant 4, lacks both exons 4 and 5, while OPN5 contains an extra exon generated from the retention of a portion of the intron 3 of the canonical isoform. This isoform 5 has a different start codon, resulting in the largest OPN transcript [5] (Fig. 1). However, differently from OPNa, OPNb and OPNc, the roles of these more recently described OPN-SIs have not yet been investigated in any tumor type.

OPN elicits different cell effects that are attributable to distinct isoforms, multiple receptors and binding sites. OPN binds to cells mainly through arginine-glycine-aspartate (RGD) and non-RGD–mediated interactions with integrins and CD44, respectively, activating multiple and varied signaling pathways [16]. OPN binds CD44 possibly via the v6 and v7 CD44 splice variants, mediating cell adhesion of a wide range of cell types resulting in distinct cellular behaviors. Binding to these different domains of OPN can control different cellular functions, such as differentiation, adhesion, migration, and apoptosis [17]. Phosphorylation also seems to be functionally important in determining whether OPN binds to cell surface receptors or to the extracellular matrix. Of note, OPN-SIs modify their phosphorylation patterns and these changes can also possibly contribute to their tissue and tumor specific roles [8].

OPN is also a substrate for extracellular proteases, including thrombin and the metalloproteinases MMP-3 and MMP-7 [16,18]. An N-terminal fragment of OPN produced by thrombin, named thrombin-cleaved OPN (trOPN), contains a “cryptic” integrin binding site, which specifically binds to $\alpha 9\beta 1$ integrin receptor. OPN can also bind to extracellular matrix proteins, such as fibronectin and collagen, as well as to calcium, modulating bone mineralization and resorption [19].

Osteopontin and hematopoiesis

Hematopoietic stem cells (HSC) are primitive cells able to reconstitute all blood cell lineages throughout the life of an individual. The microenvironment in which stem cells reside is essential for their survival, self-renewal, and differentiation. The osteoblasts, the bone-forming cells, are key regulatory components of this microenvironment, named HSC niche. Among several molecules important for this HSC niche, tOPN plays crucial roles [20,21].

As a first step to better understand the roles of OPN in HMs, we herein review OPN behaviors in the HSC niche. OPN functions in hematopoiesis are mainly based on OPN well-documented role in bone regulation. Within bone, OPN is mainly expressed at sites of bone remodeling and at cell-lined bone surfaces, such as the endosteum, where stem cells may bind this glycoprotein [22,23]. This microenvironment provides both a physical structure and the non-hematopoietic cellular and extracellular molecules of the HSC niche. Inside this environment, OPN is a key molecule promoting the attraction, retention and regulation of HSCs, which specifically binds to OPN *in vitro* via β1-integrins. Moreover, osteoblasts that participate in this HSC niche produce varying amounts of OPN in response to stimulation. In this scenario, OPN is a constraining regulator of HSC proliferation *in vivo* and *in vitro*. Additionally, it has been inhibiting differentiation *in vitro*, further evidencing that OPN

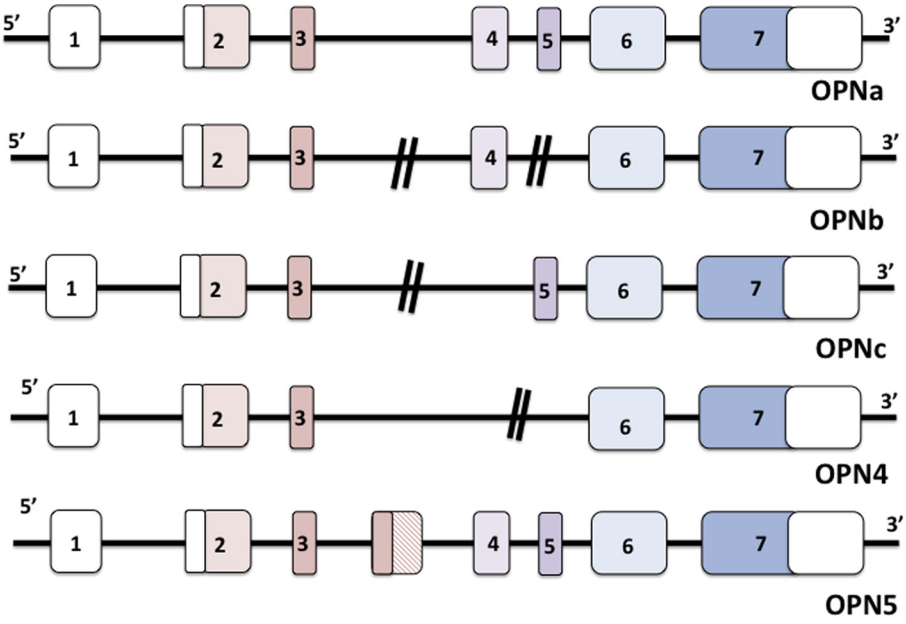

Fig. 1. OPN gene structure, described splice variants and their respective exon arrangements. The full length isoform, named OPNa, contains 7 exons represented by white (non-coding) and colored (coding) boxes. OPNb and OPNc lack exons 5 and 4, respectively, while OPN4 lacks both exons 4 and 5. Conversely, OPN-5 contains an additional exon (hatched box), located between exons 3 and 4, that results from inclusion of part of intron 3. Adapted from Briones Orta et al., 2017 [5].