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Review

Vascular calcification in type-2 diabetes and cardiovascular disease: Integrative roles for OPG, RANKL and TRAIL

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ABSTRACT

Vascular calcification (VC), a disorder that causes blood vessel hardening and dysfunction, is a significant risk factor for type-2 diabetes mellitus (T2DM), which invariably manifests associated cardiovascular complications. Although the clinical effects of VC have been well-documented, the precise cellular events underlying the manifestation and progression of VC are only now coming to light. Current research models indicate that VC likely involves signalling pathways traditionally associated with bone remodelling, such as the OPG/RANKL/TRAIL signalling system. In this respect, receptor activator of NF-κB ligand (RANKL) promotes VC whilst osteoprotegerin (OPG) acts as a RANKL decoy receptor to block this effect, events that contrast with the known functional influence of these proteins during bone metabolism. Moreover, evidence suggests that tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), an alternative decoy ligand for OPG, may exert an anti-calcific influence within the vasculature. In the current review, we conduct a timely examination of this complex VC pathology from both mechanistic and therapeutic perspectives. Our objectives are twofold: (i) to critically assess our current understanding of both osteogenic and vascular calcification pathways, with particular focus on the co-interactive roles of OPG, RANKL, and TRAIL. Extensive *in vitro*, *in vivo*, and clinical studies will therefore be reviewed and critical findings highlighted; and (ii) to examine a range of therapeutic approaches of potential relevance to VC pathology. In this regard, a clear focus on VC as it applies to T2DM and cardiovascular disease (and particularly atherosclerosis) will be maintained.

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Abbreviations: BMP, bone morphogenetic protein; CAC, coronary artery calcium; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; EC, endothelial cell; GLP-1RA, glucagon-like peptide-1 receptor agonist; MGP, matrix gla protein; MI, myocardial infarction; NF-κB, nuclear factor kappa-beta; OPG, osteoprotegerin; RANK, receptor-activator of nuclear factor kappa-beta; RANKL, receptor-activator of nuclear factor kappa-beta ligand; T2DM, type-2 diabetes mellitus; TNF, tumour necrosis factor; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; VC, vascular calcification; VSMC, vascular smooth muscle cell.

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1. Introduction

Cardiovascular disease (CVD) remains a leading cause of mortality among patients with type-2 diabetes mellitus (T2DM), in which a high prevalence of vascular calcification (VC) is a significant contributing risk factor [1]. The VC process, analogous to that of bone morphogenesis, can generally be described as a form of progressive arterial hardening that results in reduced vessel elasticity [2], ultimately increasing the risk of future cardiovascular events. There are two major forms of calcification; intimal calcification, which involves lipid and cholesterol accumulation under the damaged endothelial monolayer, and medial calcification, also known as Mönckeberg's sclerosis, which involves mineral deposition within the vessel smooth muscle layer [3]. VC conventionally affects the medial arterial layer within the T2DM population, whilst intimal calcification has long been associated with atherosclerotic disease [4]. It should be noted that, although T2DM-related calcification has been well-documented at the clinical level, the molecular mechanisms underlying the manifestation and progression of VC are still the subject of much debate. In this respect, the objectives of this review are twofold: (i) to critically assess our current understanding of both osteogenic and vascular calcification pathways, and in particular, the co-interactive roles of OPG, RANKL, and TRAIL. A joint focus will be maintained on both T2DM and atherosclerosis, linked co-morbidities manifesting medial and intimal calcification, respectively. In this regard, extensive *in vitro*, *in vivo*, and clinical studies related to both types of pathology will therefore be reviewed and critical findings highlighted; and (ii) to examine a range of therapeutic approaches of potential relevance to VC pathology.

2. Osteogenesis — the role of osteoblasts and osteoclasts

Before considering the VC process, it is critical to first understand calcification within the traditional physiological setting of bone morphogenesis. By way of overview, bone remodelling involves a complex equilibrium between anabolic bone formation and catabolic bone resorption, a key dynamic balance for healthy bone metabolism. This balance initially enables early bone development and thereafter maintains mineral homeostasis of calcium and phosphorus [5], allowing continuous removal of old or damaged bone tissue alongside simultaneous growth of new bone. There are two cell types at the forefront of bone morphogenesis, namely bone-forming osteoblasts and bone-resorbing osteoclasts, which jointly regulate the remodelling process in conjunction with various hormones and cytokines. Osteoblasts are derivatives of bone marrow stem cells, whilst osteoclasts arise from the cytoplasmic fusion of immune precursors of monocyte/macrophage lineage to generate a multi-nucleated pre-osteoclast that forms a mature osteoclast upon activation [6,7]. Over-activation of bone-resorbing osteoclasts can lead to multiple pathological conditions including osteoporosis and rheumatoid arthritis [8], whilst diminished osteoclast function may result in osteopetrosis (excessive bone formation). These respective disease processes highlight the critical importance of maintaining a healthy balance between bone formation and resorption.

Central to this osteogenic balance are the serum glycoproteins, osteoprotegerin (OPG) and receptor activator of nuclear factor kappa-B ligand (RANKL), which function as part of a signalling triad with the RANK receptor to modulate cell function, differentiation and survival during bone morphogenesis [9]. RANKL has long been implicated in the promotion of osteoclastogenesis and bone resorption [10]; this function entails binding of RANKL to its cell surface RANK receptor, which is widely expressed in both precursor and mature osteoclasts [11,12]. Within this context, OPG acts as a soluble decoy receptor for RANKL [13], preventing RANK–RANKL interactions and blocking the resulting downstream osteoclastogenic cascade (Fig. 1). Generally, when RANKL expression is induced, OPG levels are downregulated such that the RANKL:OPG ratio promotes osteoclastogenesis [8]. Interestingly, the RANKL:OPG ratio appears to be differentially regulated in pathological conditions compared to healthy physiological states [14].

RANKL is a type-II homotrimeric transmembrane protein [9] and a member of the tumour necrosis factor (TNF) superfamily. RANKL typically remains membrane bound, but also exhibits at least two known active soluble forms that may arise either through proteolytic cleavage from the cell membrane or alternate mRNA splicing [15]. Both membrane-associated and secreted forms of RANKL are capable of promoting osteoclast formation [16]. Structurally, RANKL has a small intracellular N-terminal domain, a transmembrane anchor, a connecting stalk and an extracellular receptor-binding domain, the latter of which typically arranges into a homotrimer in both membrane-bound and soluble form [13]. Whilst many cell types express RANKL, osteocytes appear to be the prominent source for *in vivo* activation of osteoclast precursors [17] (Fig. 1). Interestingly, RANKL is also expressed by osteoblasts, a process stimulated by many of the same factors that stimulate osteoclastogenesis and osteoclastic activity [9]. Additional sources of RANKL include vascular cells, stromal cells, T-cells and immune osteoclast precursors (monocytes, macrophages and dendritic cells) [18–20].

OPG, the decoy receptor for RANKL, is a soluble TNF receptor family member often referred to as an "osteoclastogenesis inhibitory factor" [21]. OPG is synthesized and secreted *in vivo* by most cell types, but osteoblasts and stromal cells exhibit the most prominent expression [20]. Structurally, OPG is a glycosylated cytokine with seven domains; four cysteine-rich domains (1–4) at the N-terminus are responsible for attenuating RANKL-induced osteoclast activation and activity [13], while domains 5 and 6 are apoptosis-mediating regions. Domain 7 is responsible for cysteine-mediated dimerization, and can also bind the anticoagulant heparin [22]. OPG is, however, an unusual member of the TNF receptor superfamily, as it lacks a transmembrane region and is exclusively secreted as a soluble protein [13]. OPG exists in serum as either a 60 kDa monomer or a 120 kDa disulphide-linked homodimer, with the latter more biologically active; it can also be detected in complex with any one of its ligands [23]. While RANKL and OPG play key roles in bone turnover, they are also central to the mechanisms involved in vascular calcification.

3. Vascular calcification (VC)

For many years, the advancement of VC was considered to be due to a passive deposition of calcium along the vessel wall. However, it is now known to be a highly dynamic process involving the action of hormones

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