# Vascular Calcification

Subjects: Immunology | Pathology
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A variety of actively regulated processes on cellular and systemic level with various contributing and inhibiting factors can result in vascular calcification (VC). Currently, treatment is limited to management of risk factors including regulation of the calcium-phosphate metabolism. Due to the complex pathophysiology, the mechanisms underlying ectopic calcification are studied in various, distinctly different research models. Beside in vitro models using cells of different origin, ex vivo settings using aortic tissue are available. In addition, various in vivo disease-induced animal models are currently used in research. All of these experimental settings depict (patho)physiologic mechanisms within the vascular calcification process.

Keywords: calcification ; research models ; in vitro ; ex vivo ; in vivo ; mineralization

## 1. Introduction

The pathophysiology of VC is characterized by alterations of the vessel wall and dysregulation of mineralization inhibitors, ending in calcification of the media by mechanisms comparable to bone formation. Abnormal metabolic conditions such as uremia in the context of chronic kidney disease [1], impaired bone metabolism with hyperphosphatemia [2], hypercalcemia and diabetes mellitus type 2 [3][4] lead to medial located calcification and depict the idea of a systemic disease. This is further supported by a decrease in plasma concentrations of endogenous inhibitors of ectopic calcification like fetuin-a, matrix gla protein (MGP) and inorganic pyrophosphate (PPi) [5][6].

## 2. Vascular Calcification - Current Research Models

The vascular smooth muscle cell (VSMC) in the media of the vessel wall is one pivotal player in vascular calcification. A variety of conditions like inflammation [7], reactive oxygen species (ROS) [8][9] and senescence [10] induce a phenotype shift of the contractile VSMC to a synthetic state. Extracellular deposits such as matrix vesicles or apoptotic bodies from VSMC serve as a nucleation site for hydroxyapatite and therefore promote calcification [11][12][13]. Degradation of the extracellular matrix (ECM) by matrix metalloproteinases (MMP) facilitates hydroxyapatite deposition and osteoblastic trans-differentiation of VSMC [14]. Aside from that, other cell types are involved: mesenchymal osteoprogenitor cells, hematopoietic progenitor cells, endothelial progenitor cells and myeloid cells are circulating cells bearing osteogenic and calcifying potential [15].

This vast variety of influencing factors in the development of VC reflect, at least in part, the diversity of research models and vice versa. Therefore, studying vascular calcification entails the challenge of utilizing a manageable experimental setting reducing the complexity of its pathophysiologic interrelations while still representing a physiological setting.

The recent entry [16] summarizes various cell types and experimental conditions for in vitro settings, currently available ex vivo protocols and different in vivo models using rats and mice with their limitations and advantages. The in vivo models are structured according to their background setting into naturally occurring and genetically modified models and depends on the induction of disease state into operation, substance application and special diet. In vitro models allow studying the signaling pathway under manageable conditions; however, provide the most non-physiological environment. Ex vivo settings using vessel tissue meet this drawback at least partly and might bridge the gap to in vivo models. While offering a natural environment, in vivo models require massive interventions to achieve the vascular calcification condition.

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