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Functional role of inorganic trace elements in angiogenesis—Part I: N, Fe, Se, P, Au, and Ca

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Summary

Many inorganic elements are recognized as being essential for the growth of all living organisms. Transfer of nutrients and waste material from cells and tissues in the biological systems are accomplished through a functional vasculature network. Maintenance of the vascular system is vital to the wellbeing of organisms, and its alterations contribute to pathogenesis of many diseases. This article is the first part of a review on the functional role of inorganic elements including nitrogen, iron, selenium, phosphorus, gold, and calcium in angiogenesis. The methods of exposure, structure, mechanisms, and potential activity of these elements are briefly summarized. An electronic search was performed on the role of these elements in angiogenesis from January 2005 to April 2014. The recent aspects of the relationship between different elements and their role in angiogenesis, and production of pro- and anti-angiogenic factors were assessed. Several studies emphasized the role of these elements on the different phases of angiogenesis process in vivo. These elements can either enhance or inhibit angiogenesis

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events. Nitrogen in combination with bisphosphonates has antiangiogenic effects, while nitric oxide promotes the production of angiogenic growth factors. Iron deficiency can stimulate angiogenesis, but its excess suppresses angiogenesis events. Gold nanoparticles and selenium agents have therapeutic effects due to their anti-angiogenic characteristics, while phosphorus and calcium ions are regarded as pro-angiogenic elements. Understanding how these elements impact angiogenesis may provide new strategies for treatment of many diseases with neovascular component.

Keywords: Angiogenesis; Endothelial cells; Inorganic elements; Wound healing

1. Introduction

The necessity to recognize and concentrate on health risks associated with inorganic pollutants, toxic metals, and radioactivity have become highly evident. This is further emphasized as the impact of human activities and issues of environmental health become increasingly global in scale and extent. The associations between environmental pollutants and health outcomes are complex and often poorly understood [1]. A schematic of the effect of activities and pollutant on human health is presented in Fig. 1. Many studies indicate that the role of environment including diet, pollutants, and contamination may account for 90–95% of all cancer cases, whereas genomic changes only account for less than 10% [2]. Thus, certain essential trace elements exist in nature whose level is influenced by environmental factors that may enhance or jeopardize human health. Their concentrations are regulated through homeostatic mechanisms and if they pass the inhibitory thresholds they often become toxic [3,4]. Thus, understanding the role of trace elements on human body, especially in the processes like angiogenesis, is crucial. Hyper- or hypo- vascularization could result in onset and progression of kidney complications, cardiovascular disease, diabetic retinopathy, stroke, and cancer [5–8]. Previous studies have revealed that most woman 40–50 years of age, who did not have cancer-related disease in their life-time, have micro cancer cells in their breast. In addition, all autopsied individual males 50–70 years of age, have in situ carcinomas in their thyroid gland, but they are not in danger without angiogenesis [9]. However, angiogenesis is the main constituent of regeneration and regulates repair processes.

The two major processes that play important roles in life expectancy, cancer, and regeneration are influenced by angiogenesis. According to last figures, it is estimated that more than 1·6 million new cancer cases will be diagnosed, and approximately more than 0·5 million cancer deaths will occur in the US in year 2014. Approximately, one fourth of death in the US is related to cancer, which makes it the second most common cause of death. Taking this volume of death into account, the significance of investigating cancer and its related parameters is obvious [10]. Accordingly, by more than $4 billion investment in angiogenesis research and in the development of antiangiogenic drug-based therapies, angiogenesis has become one of the most funded area of research in the history of human medical research [11]. In Western nations, more than 489 million patients could benefit from some forms of antiangiogenic and/or proangiogenic therapies [11]. Thus, understanding angiogenesis mechanisms and regulators may significantly influence the rate of cancer related death through affecting the blood vessel networks reconstructing and spreading out [12,13]. Angiogenesis is associated with developmental and repair process of vascular networks from endothelial progenitor cells that differentiate into endothelial cells (EC) [14]. Angiogenesis and arteriogenesis/vascular remodeling represent excellent therapeutic options for numerous cardiovascular diseases.

The interest in use and application of inorganic chemistry and trace elements in medicine continues to expand. Major international conferences such as the International Conference on Bioinorganic Chemistry and the European Conference on Bioinorganic Chemistry now contain a significant fraction of presentations dedicated to 'Inorganic Trace Element in Medicine'. Recent dedicated volumes or sections in Metal Ions in Biological Systems, Chemical Reviews, and Coord Chem Rev further testify to the growing importance of the discipline. As such, it is important to categorize and quantify major areas of research to diagnose new intentions and possibilities for intervention.

There are several trace elements which are involved in promotion and stabilization of new blood vessels such as nitrogen, iron, selenium, gold, and others [15–17]. The current article is the first part of a review series in this issue discussing the role of these elements in angiogenesis and vascular biology.

2. Materials and methods

2.1. The purpose of review

Information regarding the role of inorganic elements in angiogenesis is limited. This literature review was aimed to evaluate the key role of inorganic elements and their possible mechanism of action; specifically the potential effects of nitrogen, iron, selenium, phosphorous, gold, and calcium elements in angiogenesis.

2.2. Inclusion and exclusion criteria

All articles in peer-reviewed journals, published in English from January 2005 to April 2014, were included in this review. Other investigations, which did not include these criteria, were excluded.