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Review

Green tea and its anti-angiogenesis effects

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ABSTRACT

The development of new blood vessels from a pre-existing vasculature (also known as angiogenesis) is required for many physiological processes including embryogenesis and post-natal growth. However, pathological angiogenesis is also a hallmark of cancer and many ischaemic and inflammatory diseases. The pro-angiogenic members of the VEGF family (vascular endothelial growth factor family), VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PlGF), and the related receptors, VEGFR-1, VEGFR-2 and VEGFR-3 have a central and decisive role in angiogenesis. Indeed, they are the targets for anti-angiogenic drugs currently approved. Green tea (from the Camellia sinensis plant) is one of the most popular beverages in the world. It is able to inhibit angiogenesis by different mechanisms such as microRNAs (miRNAs). Green tea and its polyphenolic substances (like catechins) show chemo-preventive and chemotherapeutic features in various types of cancer and experimental models for human cancers. The tea catechins, including (−)-epigallocatechin-3-gallate (EGCG), have multiple effects on the cellular proteome and signalome. Note that the polyphenolic compounds from green tea are able to change the miRNA expression profile associated with angiogenesis in various cancer types. This review focuses on the ability of the green tea constituents to suppress angiogenesis signaling and it summarizes the mechanisms by which EGCG might inhibit the VEGF family. We also highlighted the miRNAs affected by green tea which are involved in anti-angiogenesis.

1. Introduction

Angiogenesis is the generation of new blood vessels from a pre-existing vasculature [1]. Angiogenesis is divided into two components: physiological and non-physiological or pathological angiogenesis. Physiological angiogenesis occurs during various processes such as wound healing, tissue remodeling, luteinisation of the follicle in the ovary, placental development and pregnancy establishment. Pathological angiogenesis is a hallmark of many ischaemic and inflammatory diseases (*e.g.* endometriosis, psoriasis, rheumatoid arthritis (RA), neovascular age-related macular degeneration of the eye, diabetic retinopathy) and cancer growth and metastasis [2]. Under physiological conditions, angiogenesis is highly regulated by the balance between a huge number of pro- and antiangiogenic factors [3]. There is currently great interest in the use of nutraceuticals, *i.e.* plant chemicals used as ingredients of foods and drinks.

Green tea (from the Camellia sinensis plant) is one of the most popular beverages worldwide and its consumption has an effect on many diseases. Green tea consuming populations have been examined in several (pre)clinical studies [4–7].

It has been revealed that the green tea catechins not only possess anti-inflammatory and anti-oxidative-stress activities but they have also shown anti-carcinogenic, anti-microbial, anti-obesity and anti-diabetic properties [8]. The main catechins found in green tea are (−)-epigallocatechin-3-gallate (EGCG), epicatechin gallate (ECG), epigallocatechin (EGC) and epicatechin (EC) [9], gallocatechin gallate (GCG), catechin gallate (CG) and cathecin (CT) [10]. EGCG is the most abundant and active catechin in green tea, accounting for 50–80% of the catechin content [11]. Green tea polyphenols inhibit cell proliferation and present a strong antiradical activity [12].

Some evidences indicated that EGCG could protect cells from tumor development through the enhancement of gap junctional communication between cells.

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It was observed that polyphenols and various components present in Green tea exert their effects by various mechanisms. One of the main mechanisms is blocking the promotion of tumor growth by sealing receptors in the affected cells. Another one implies that this substance may aid direct binding to some carcinogens [13]. Some reports indicated that EGCG is able to induce cell growth arrest and apoptosis by regulating the expression of some regulatory proteins, suppressing NF-κB activation and activating killer caspases [14]. In addition, it was observed that EGCG could inhibit matrix metalloproteinase activity. Matrix metalloproteinase could contribute to tumor cell invasion and angiogenesis [15].

Pharmacokinetic studies indicated that a daily dosage of 800 mg/day of EGCG for up to 4 weeks could be safe and well-tolerated [16,17]. On other hand, high-dose oral green tea extract and EGCG could be associated with hepatotoxic effects in rats. Therefore, Green tea and its components such as catechins could be a safe option for treatment of various diseases such as cancer, diabetic, cardiovascular, and anogenital warts [17].

Among different receptors affected by green tea constituents, microRNAs (miRNAs) have emerged as a new class of molecules that are involved in various molecular and cellular pathways [18]. This study focuses on the cellular/molecular pathway of anti-angiogenic properties of green tea especially EGCG, as well as on various miRNAs involved in these mechanisms.

1.1. Activators and inhibitors of angiogenesis

So far, many growth factors have been characterized and shown to have angiogenic activities. This includes fibroblast growth factor (FGF), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), angiopoietin/endothelial tyrosine kinase (ANG/TIE), ephrin (EPH), cadherin and semaphoring [19]. The receptor protein-tyrosine kinase and the vascular endothelial growth factor/VEGF receptor (VEGF/VEGFR) families are involved in neovascularization and angiogenesis. The VEGF/VEGFR family is the key regulator of vascular development which is the main focus of this review. The ANG/TIE system controls vascular remodeling [20] while the EPH system regulates the positioning and segregation of arterial and venous endothelial cells during development [21]. Because the members of the VEGF family and their receptors have a crucial role in formation of blood vessels, anti-angiogenic therapies are focused on developing molecules which target these factors [22].

2. VEGF family

The VEGF family plays a key role in vasculogenesis, angiogenesis and lymphangiogenesis. The human VEGF family comprises of five members including VEGF (or VEGF-A), VEGF-B, VEGF-C, VEGF-D and placental growth factor (PlGF) Multiple isoforms of VEGF, VEGF-B, and PlGF are generated through alternative splicing of their corresponding immature mRNAs.

Three members of the VEGF family have receptor protein-tyrosine kinase activity including VEGFR1 (also known as Flt-1), VEGFR2 (also known as Flk-1 in mice and KDR in human), VEGFR3 (also known as Flt-4) and two non-enzymatic receptors (neuropilin-1 and -2). These receptors are composed of three different domains including IgG-like extracellular domains, a transmembrane domain and a cytoplasmic tyrosine kinase domain. The activity of these VEGFs is further modulated by some ligands such as co-receptors (*e.g.* heparan sulfate, neuropilins and integrins) [22]. Except for the VEGF-C, VEGF-D and VEGFR-3 that are responsible for lymphangio-genesis, the other members and receptors of the same family are involved in new blood vessel formation (Fig. 1) [23].

3. VEGF receptors

3.1. VEGFR1 (Flt-1)

VEGFR1 (Flt-1, fms-like tyrosyl kinase-1, where fms refers to feline McDonough sarcoma virus) has an ability to bind to VEGF, PlGF and VEGF-B (Fig. 2) [24–26]. The developmental stage and location of endothelial cells expressing VEGFR1 determines various functions of this receptor [27].

Note that VEGF has higher affinity for VEGFR1 than VEGFR2 (approximately ten-fold higher affinity) [24,27,28]. Unlike VEGFR2, VEGFR1 has weak tyrosine kinase phosphorylation activity following stimulation by VEGF [24]. Although activation of VEGFR1 has no direct proliferative or cytoskeletal effects [24], it leads to increased expression and activity of urokinase type plasminogen activator and plasminogen activator inhibitor-1 in endothelial cells [26]. These molecules play a role in extracellular matrix degradation and cell migration.

The human VEGFR1 gene has 30 exons. The alternative transcripts encode two isoforms: (I) Soluble VEGFR-1 (sVEGFR-1) which binds to and inhibits the action of VEGF. This receptor has no transmembrane (TM) and cytoplasmic kinase domains. (II) A

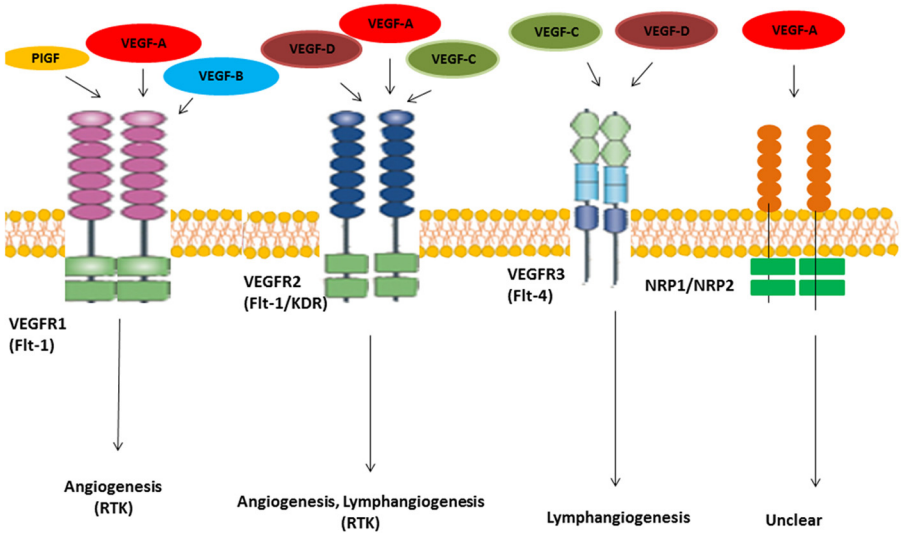

Fig. 1. Various VEGFs and their receptors.