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MINI REVIEW

# Targeting of histamine producing cells by EGCG: a green dart against inflammation?

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**Abstract** The human body is made of some 250 different cell types. From them, only a small subset of cell types is able to produce histamine. They include some neurons, enterochromaffin-like cells, gastrin-containing cells, mast cells, basophils, and monocytes/macrophages, among others. In spite of the reduced number of these histamine-producing cell types, they are involved in very different physiological processes. Their deregulation is related with many highly prevalent, as well as emergent and rare diseases, mainly those described as inflammation-dependent pathologies, including mastocytosis, basophilic leukemia, gastric ulcer, Crohn disease, and other inflammatory bowel diseases. Furthermore, oncogenic transformation switches some non-histamine-producing cells to a histamine producing phenotype. This is the case of melanoma, small cell lung carcinoma, and several types of neuroendocrine tumors. The bioactive compound epigallocatechin-3-gallate (EGCG), a major component of green tea, has been shown to target histamine-producing cells producing great alterations in their behavior, with relevant effects on their proliferative potential, as well as their adhesion, migration, and invasion potentials. In fact, EGCG has been shown to have potent anti-inflammatory, anti-tumoral, and anti-angiogenic effects and to be a potent inhibitor of the histamine-producing enzyme, histidine decarboxylase. Herein, we review the many specific effects of EGCG on concrete molecular targets of histamine-producing cells and discuss the relevance of these data to support the potential therapeutic interest of this compound to treat inflammation-dependent diseases.

**Keywords** EGCG · Histamine-producing cells · Inflammation

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## Introduction

Inflammation is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a protective attempt by the organism to remove the injurious stimuli as well as to initiate the healing process for the tissue. Inflammation is normally tightly regulated by interaction between mediators of inflammation and inflammatory cells and errors in the system cause many complex diseases (e.g., sepsis, infectious diseases, trauma, asthma, allergy, autoimmune disorders, transplant rejection, cancer, neurodegenerative diseases, obesity, and atherosclerosis) [57].

Cytokines represent a group of small polypeptides involved in many steps of the inflammatory response. They form a complex and redundant network with pleotropic activity and functional redundancy [22]. Cytokines are produced by both resident and migrating cells, such as mast cells, macrophages, and neutrophils, and after release, they can act either locally or systemically.

## Green tea composition

Tea is the second beverage most consumed in the world after water. It is a product made up from leaves and buds of *Camellia sinensis*. There are different types of tea depending on manufacturing process: white tea is the uncured and unfermented tea leaf, green tea is "non-fermented," oolong tea is "semi-fermented," and black or red tea is "post-harvested fermented" before drying and steaming. Tea consumption is part of many people daily routine, as an everyday drink and as a therapeutic aid in many illnesses. Chinese have known about the medicinal benefits of green tea since ancient times, using it for treatment of headaches, body aches and pains, digestion, depression, detoxification, as an energizer and, in general, to prolong life. In recent years, the legendary medicinal properties of tea have been given serious scientific support.

Tea is a natural source of the amino acid theanine, methylxanthines such as caffeine and theobromine, and polyphenolic antioxidant. Polyphenols constitute the most interesting group of green tea components and green tea can be considered an important source of polyphenols, particularly flavonoids. The main flavonoids present in green tea are catechins (flavans-3-ols). There are four major catechins: (–)-epigallocatechin-3-gallate (EGCG; approximately 59% of total catechins), (–)-epigallocatechin (EGC; 19% approximately), (–)-epicatechin-3-gallate (ECG, 13.6% approximately), and (–)-epicatechin (EC; 6.4% approximately) [10].

## Properties of green tea in human health

In vitro and animal studies provide strong evidence that green tea polyphenols may play a role in the risk and pathogenesis of several chronic diseases, especially cardiovascular disease and cancer, and related pathologies. In addition, several studies suggest a beneficial impact of green tea intake on bone density, cognitive function, dental caries, and kidney stones, among other effects [45, 64]. Over the last years, numerous epidemiological and clinical studies have revealed several physiological responses to green tea which may be relevant to the promotion of health and the prevention or treatment of some chronic diseases [27, 38]. It has biological and pharmacological properties such as anticarcinogenic, antimetastatic, antioxidative, antihypertensive, and anti-hypercholesterolemic activities [8, 11, 13, 24, 34, 42, 58, 59]. Major principles for these activities were shown to be catechins. These polyphenols are antioxidant in nature and have been shown to function as anti-inflammatory and anticarcinogenic agents in various biological systems [29, 63]. EGCG, the most abundant polyphenol in green tea leaves, is believed to be the most responsible compound for the health benefits attributed to tea [20].

Several studies showed that EGCG induces apoptosis and cell cycle arrest in tumor cells [21, 56], inhibits urokinase activity [28], matrix metalloproteinases, and urokinase-plasminogen activator [23], cell proliferation [4, 32], lipoxygenase, and cyclooxygenase activities [25, 54], and the expression of angiogenesis related genes [47].

## Modulation of inflammation pathways by EGCG

Several studies demonstrate that EGCG can modulate multiple signal transduction pathways in a way that suppresses the expression of inflammation mediators.

- Effect of EGCG on nuclear factor-kappa B (NF–κB) signaling pathway. EGCG inhibits NF–κB activity by blocking the phosphorylation of IκB–α [1, 40, 60]. This inhibition results in the decrease in the expression of inflammatory genes products including lipoxygenase [66], cyclooxygenase [37], NO synthase [12], and TNF-α [67].
- Effects of EGCG on mitogen activated protein kinases (MAPKs) and activator protein-1 (AP-1) pathways. EGCG exerted a marked inhibition of both basal and IL-1-stimulated MAPKs phosphorylation [6] and suppressed the RANKL-induced activation of JNK pathway [36]. EGCG was also found to inhibit the DNA binding activity of AP-1 in human chondrocytes [6].

- Effects of EGCG on signal transducers and activators of transcription (STAT) pathway. EGCG exert a potent and specific inhibitory effect on STAT1 activation in a number of human cell types [49, 62]. Moreover, it was reported that EGCG can suppress STAT-3 phosphorylation in human gingival [26] and fibroblasts [53].
- Effects of EGCG on inflammatory cytokines and chemokines expression. EGCG has been shown to inhibit the TNF-α gene expression and its secretion in different cell types [14]. EGCG has also been shown to downregulate IL-1β-induced RANTES and GRO-α production in human fibroblast [2] and MCP-1 expression in fibroblasts [2], monocytes, and macrophages [47, 48].
- Antioxidant effects of EGCG. Investigations from a number of laboratories have demonstrated that green tea polyphenols are efficient free radical and singlet oxygen scavengers [33]. EGCG also considerably increased the gene expressions of catalase, superoxide dismutase, and glutathione peroxidase activities which are essential components of a robust antioxidant defense system [50].
- Induction of apoptosis and cell cycle arrest by EGCG. EGCG has been shown to affect a number of factors associated with cell cycle progression, but the direct inhibition of cyclin-dependent kinases is considered the primary event. This inhibition could be the consequence of the induction of various negative regulators of the cell cycle. EGCG also induces the expression of p21 and p27 while decreasing the expression of cyclin $D_1$ and the phosphorylation of retinoblastoma [35].

## Effects of EGCG on histamine handling cells

Histamine is a biogenic amine with a major role in different physiological function such the contraction of smooth muscles, increase in vascular permeability, stimulation of gastric acid secretion, neurotransmission, immunomodulation, proliferation, etc [7, 9]. Among all the cell types of the human body, only a small subset of cell types is able to produce histamine. They include some neurons, enterochromaffin-like cells, gastrin containing cells, mast cells, basophils, and monocytes/macrophages, among others. Herein, we briefly summarize what is currently known concerning molecular targets of EGCG in these histamine handling cells.

### Cells from the immune/inflammatory axis

Besides studies on cancer cells, the most abundant and extensive studies of EGCG effects on molecular targets have been carried out with cells from the immune/inflammatory axis.

- Megakaryocytes. EGCG has been shown to increase megakaryocyte and platelet numbers in cultures supplemented with thrombomopoietin, a central regulator of megakaryocytopoiesis and platelet production. Furthermore, EGCG also exerts a clear radio-protective effect on this cell lineage [51].
- Monocytes/macrophages. It has been shown that EGCG is capable of modulating radical oxygen species production during respiratory burst of rat macrophages. In this and other cases, EGCG acts as an effective superoxide anion scavenger [5]. An indirect effect of EGCG on monocyte/macrophage physiology is the inhibitory effect caused on endothelial VCAM-1, which is accompanied by a decreased monocyte adhesion to endothelial cells [41]. On the other hand, EGCG specifically promotes monocyte apoptosis [30]. Recently, EGCG has been shown to inhibit the late pro-inflammatory cytokine HMGB1 (high mobility group box 1) release by monocytes/macrophages upon stimulation of bacterial endotoxin. This, in turn, gives rise to a rescue of mice from lethal sepsis [39]. Furthermore, EGCG has also been shown to inhibit intracellular survival of pathogenic bacteria within macrophages [31]. More recently, our group has been shown that treatment of THP-1 cells with EGCG decreased MCP-1 and CCR2 gene expression, together with MCP-1 secretion and CCR2 expression at the cell surface. EGCG also inhibited beta1 integrin activation. The effects on these molecular targets were in agreement with the EGCG-induced inhibition of THP-1 migration in response to MCP-1 and adhesion to fibronectin [48].
- Basophilic cells. A well-known direct molecular target of EGCG is the high-affinity IgE receptor FcεRI. In fact, FcεRI expression in basophilic cells is suppressed by EGCG [15, 16]. More recently, the 67-kDa laminin receptor has been shown as another

direct molecular target for EGCG and a determinant of its degranulation inhibitory and anti-allergic effects [17–19]. Very interestingly, this 67-kDa laminin receptor is metastasis-associated and confers EGCG responsiveness to cancer cells at physiologically relevant concentrations [61].

- Mast cells. Histamine is a key mediator of allergic and inflammatory responses. This biogenic amine is produced in a reaction catalyzed by histidine decarboxylase (HDC) [46]. EGCG targets histamine at two levels. On the one hand, EGCG has been shown to inhibit mast cell degranulation [65]. On the other hand, our group firstly demonstrated a potent inhibitory effect of EGCG on HDC activity [55]. Very recently, our results have been confirmed by an independent study showing that, in fact, among 22 tested food components, EGCG (along with epicatechin gallate) was the most effective inhibitor of HDC [52]. On the other hand, another recent study carried out by our group has shown that, among others, EGCG reduces the expression of the integrins α5 and β3, as well as that of the chemokine MCP1 (monocyte chemoattractant protein 1), giving rise to a lower adhesion and migration of mast cells, associated with a decreased potential to produce signals eliciting monocyte recruitment [47].

Neurons and other histamine-handling cells

For histamine-handling neurons, EGCG has been shown to exert multifunctional effects, including neuroprotection, metal-chelatin-radical scavenging, and anti-inflammation [3, 43, 44].

Neuroendocrine cells secreting gastrin and/or biogenic amines in the stomach are most probably cellular targets for the action of EGCG. However, this research topic remains to be studied, with the exception of some articles describing the protective effect of EGCG against *Helicobacter pylori*-induced gastric epithelial cytotoxicity and the inhibitory effect of EGCG against gastric cancer cell proliferation and angiogenesis [68].

## Pathobiological relevance

There is increasing evidence pointing to the beneficial anti-inflammatory effects of EGCG. They include its neuroprotective and radio-protective actions, its potent inhibitory effect on cytokine and chemokine release, its molecular targets leading to monocyte apoptosis, mast cell degranulation inhibition, HDC activity inhibition, as well as its interference with mast cell adhesiveness, migration, and monocyte recruitment. All these effects point to EGCG as a very promising anti-inflammatory agent with potential pharmacological interest to be evaluated in clinical trials. However, further in-depth mechanistic studies in vitro and appropriate and relevant animal model studies in vivo are needed together in order to fully appreciate the value of EGCG in inflammation and other aspects of human health and diseases in the future.

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