Medical Research Archives

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OPEN ACCESS

Published: July 31, 2022

**Citation:** Roni Aloni, 2022. What can we learn from the hormonal mechanisms and tumor- inducing bacteria that regulate vascular differentiation and cancer in plants?, Medical Research Archives, [online] 10(7). https://doi.org/10.18103/mra.v10i7.2973

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DOI
https://doi.org/10.18103/mra.v10i7.2973

ISSN: 2375-1924

REVIEW ARTICLE

# What Can We Learn from The Hormonal Mechanisms and Tumor- Inducing Bacteria That Regulate Vascular Differentiation and Cancer in Plants?

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ABSTRACT
Plants and human beings develop vascular tissues that enable their growth and function. Auxin (IAA) in plants, and vascular endothelial growth factor (VEGF) in humans, are the major signaling molecules that induce and regulate vascular development in both normal and cancer tissues. Mechanisms that induce vascular tissues in plants are discussed, aiming to stimulate similar advanced medical research in the human body. The focus is on organized and cancerous vascular differentiation, regulation of vein pattern formation, and the control of vessel diameter by hormonal gradients. Moreover, to understand the involvement of bacteria in cancer development in both plants and humans, for developing combined novel cancer therapy treatments in human beings with antibiotics and jasmonates.

**Keywords:** angiogenesis, auxin (IAA), blood vessels, cancer, cancer-inducing bacteria, jasmonate, pattern formation, tumor microbiome, vascular differentiation, vascular regeneration, vasculogensis, VEGF, vessels

**Abbreviations:** cancer stem cells (CSCs), endothelial cells (EC), methyl jasmonate (MeJA), auxin, indole-3-acetic acid (IAA), vascular endothelial growth factor (VEGF)

## 1. Introduction

The purpose of this paper is to stimulate creative thinking in human medical research inspired by findings in plants. A few basic developmental patterns in the vascular tissues of plants that are induced and regulated by hormonal signals[1] will be presented and discussed, in order to promote advanced medical research and practice in the human body.

The paper exposes the reader to concepts and hypotheses that were developed for understanding normal and cancerous vascular differentiation in plants. It is suggested that these concepts and ideas might be relevant for studying vascular development in the human body, and therefore they are discussed here, in order to promote novel ideas and advanced research in human beings.

The focus in this review is on **vessels**, which are water-conducting ducts in plants. These conduits are composed of numerous vessel elements connected end- to-end by openings (perforation plates) and limited in length by imperforated walls at both edges. Water starts to flow inside a vessel only after the vessel elements lose their cytoplasm. Vessel dimensions are important parameters for understanding long-distance water and mineral transport, vascular pathology, adaptation and evolution.[1] An increase in vessel diameter markedly increase the efficiency of water transport, owing to decrease in resistance to flow, whereas increase in both width and length decreases safety of water conduction.[2]

The vessels of plants are compared to **blood vessels**, as an artery or vein, that transport and circulate blood along the human body. A blood vessel is characterized by the vascular endothelium, a monolayer of endothelial cells (EC), which constitutes the inner cellular lining of arteries, veins and capillaries and therefore is in direct contact with the components and cells of blood.

ECs are polarized living cells: their luminal membrane is directly exposed to the circulating blood, while the basolateral surface is separated from surrounding tissues by a glycoprotein basement membrane, secreted by the ECs. The endothelium is not only a mere barrier between blood and tissues, but can also function as an endocrine organ.[3]

## 2. The primary signals that control vascular differentiation in plants

The major signalling molecules that induce and regulate vessel differentiation in plants are the hormonal signals. Plant hormones regulate gene expression, cellular activity, cell and tissue polarity, growth and differentiation of tissues, organs and the whole plant development. The hormones can be produced in any living plant cell at extremely low concentrations. They may act locally or at a distance from the producing cells. Similar to the movement of human growth factors and hormonal signals in the bloodstream to tissues and organs, plant hormones move preferably in the vascular tissues. In this review, the role of the plant hormonal signals: auxin, cytokinin, ethylene and jasmonate will be discussed.

Auxin, Indole-3-acetic acid (IAA), is the primary hormonal signal that induces vascular tissues in plants.[1] The auxin can be compared to the vascular endothelial growth factor (VEGF), which is the primary regulator of angiogenesis in human beings, in both organized tissues[4] and solid cancerous tissues.[5]

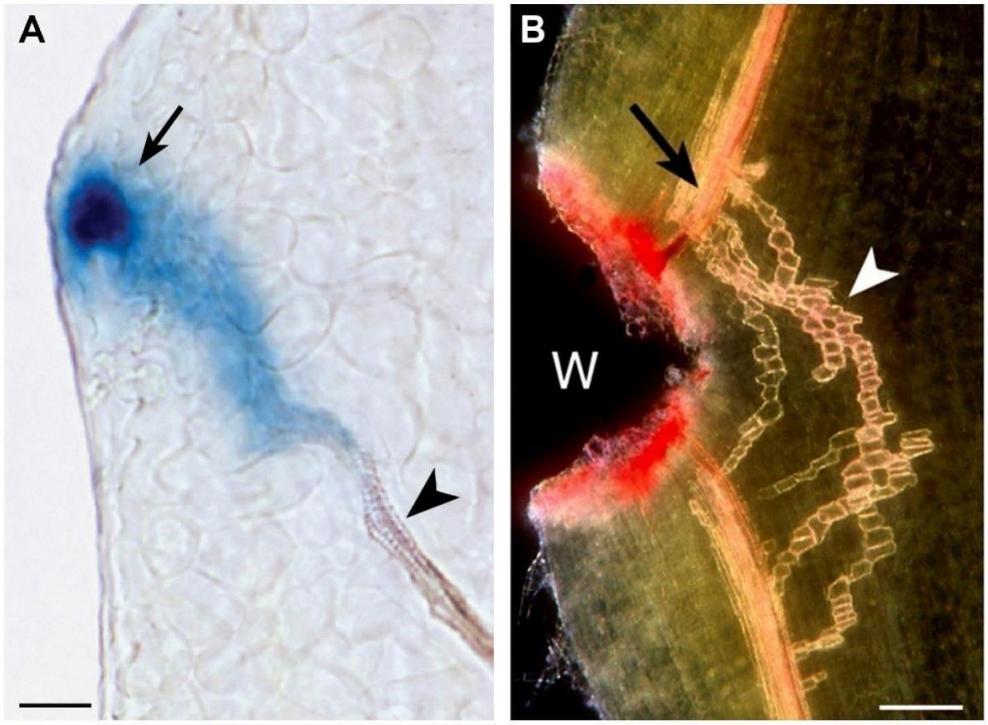
The IAA is synthesized in young growing leaves, developing flowers, seeds and fruits[1,6,7,8,9]; as well as in roots by the TAA/YUC pathway, when shoot-derived auxin is not sufficient to support root growth.[10] The continuous polar transport of IAA from the tips of young shoot organs downward to the root tips induces and regulates vascular differentiation along the plant.[1,11,12,13]

## 3. The *canalization hypothesis* explains organized vascular development

On the basis of elegant experimental evidence, Sachs[11] explained the orderly pattern of vascular tissues from leaves to roots by the *canalization hypothesis*. According to this hypothesis, IAA flow which starts by diffusion, induces a polar auxin transport process which promotes IAA movement and leads to the canalization of the auxin flow along a narrow file of cells (**Figure 1A**). These cells become more polarized and more efficient transporters of auxin. As the auxin flow becomes diverted into the canalized file, lateral neighbouring cells would receive decreasing amounts of the hormone. The continuous polar transport of auxin through the canalized cells induces a further complex sequence of events which terminates in the formation of a vessel.[11] Thus, the hypothesis proposes a positive feedback relation between the transport of the auxin signal and cell polarization: auxin transport itself induces both new and continued polarization, while cell polarity determines oriented auxin transport. The passage of auxin through a vascular bundle keeps the tissue polarized along the axis of this bundle. Polarized cells are not labile to the influence of an inductive source of auxin coming from another

direction. Therefore, when auxin is applied laterally near a longitudinal vascular bundle, the applied signal flow and the attachment of its induced new bundle to a longitudinal bundle may be delayed, or prevented (demonstrated in[14]; and in[1], see Fig. 3.7), according to the amount of auxin flowing through the longitudinal preexisting bundle. The *canalization hypothesis* provides the tools for understanding how the process of progressively improved pathways of a signal transport induces the differentiation of new vessel patterns along the intact vascular system and also around wounds (**Figure 1B**) to connect the leaves with the roots. The hypothesis was confirmed experimentally in a few vascular systems.[1]

**Figure 1:** Differentiation and regeneration of vessels induced by auxin




(A) Micrograph of a cleared leaf primordium of DR5::GUS transformed *Arabidopsis thaliana* demonstrating how the bioactive auxin hormone, namely, indole-3-acetic acid (IAA) induces a major bundle of vessels, visualizing the physiological process by the blue staining of *DR5::GUS* expression during early leaf morphogenesis. At the lobe of a young leaf primordium, showing a center of strong expression (*arrow*) marking the synthesis site of high-auxin concentration, from which the auxin starts to flow in a diffusible pattern mainly downward and gradually becomes canalized to a narrow stream that induces the vessels in a vascular bundle (*arrowhead*). (B) Polar pattern of regenerated vessels (*arrowhead*) revealing the pathways of the inducing polar auxin movement around a wound (w), in a decapitated young internode of *Cucumis sativus* treated with auxin (0.1% IAA in lanolin for 7 days), which was applied to the upper side of the internode immediately after wounding and removing the leaves and buds (the sources of auxin) above it. Showing a longitudinal view (observed after clearing with lactic acid, staining with phloroglucinol, and photographed in dark field) that the regenerated vessel elements (redifferentiated from parenchyma cells) formed above the wound (*arrow*), (where IAA was concentrated by the cut) differentiated close to the wound, while those below the wound differentiated at greater distances from the wound. Bars = 50 µm, from[6] (A); 500 µm, from[1] (B)

## 4. Vessel continuity

The continuity of vessel networks in the entire vascular system along the plant axis from leaves to roots results from the continuous movement of the polar auxin inducing signal, which therefore results in continuous functional vessels from the leaf's margins to the root tips.[1,11,13]

It is suggested that during vasculogensis, the continuity of the earliest developing vascular tissues in a human embryo, occurring by *de novo* production of endothelial cells, is likewise induced by a continuous signal flow, possibly VEGF, along gradients that induces blood vessels along organs

and the entire embryo. While during angiogenesis at the adult stage, which is promoted by hypoxia, a new vessel may develop from a blood vessel by VEGF signaling, resulting in vascular sprouting and the formation of a new blood vessel, which becomes connected to the existing vascular network. The formation of a continuous new blood-vessel anastomosis that connects two existing vessels indicates a canalized signal flow between these blood vessels.

Wounding a plant vascular bundle in a young stem induces the formation of a new regenerative vessel around the wound. The IAA signal, either naturally descending from the intact young leaves, or experimentally applied to the stem after the young leaves were removes, is the signal that induces the recovery of the vascular bundle (**Figure 1B**). Near young leaves, high-auxin concentrations induce narrow regenerative veins, while further away from the young leaves, low-auxin concentrations result in wider regenerative vessels.[15]

The continuity of functional regenerative blood vessels around a cut[4], or away from a growing cancer tissue in a human body[5] indicates that a moving signal induces this vessel regeneration around the wound or away from a developing cancer. VEGF is likely a primary inducing signal in this process, its production site is probably in vascular endothelial cells that promote sprouting and the formation of a new regenerative blood vessel around a wound or from a growing solid tumor.

## 5. Regulation of vein pattern formation in leaves

### 5.1 Sources of inducing signal in leaves and possibly in human hands

Leaves induce their own vascular tissues by the auxin signal they produce.[1,6,11,16,17] The IAA is primally synthesized in the leaf primordium periphery, specifically in the lobes[6,8,9] (**Figure 1A**). The lobes can be comparable to finger tips of a human embryo. Therefore, it is proposed that during vasculogensis, the fingertips of the embryonic hand are sites that produce the stimulating signal, possibly VEGF, which induces the initial blood vessels. Blood vessels that extend from the fingertips toward the heart.

### 5.2 Development of asymmetric and unpredictable vessel patterns

Although the leaves on the same shoot are identical genetically, each leaf has a different vein pattern, demonstrating their inherent developmental plasticity,[17,18] which is analogous to the different patterns of blood vessel found in the right hand *versus* the left hand of the same person. These different blood-vessel patterns likely develop in the embryo during vasculogensis, by random moving steams of an inductive signal, possibly VEGF. In many leaves, the vein network produced in their right leaf side is different from the pattern developed on the left leaf side. This asymmetric and unpredictable vein pattern is determined by random patterns of IAA production sites and flows, regulated by selection of various alternative auxin pathways during leaf development.

Nevertheless, there is a general regularity in vein pattern formation in leaves where high-auxin concentrations at the leaf periphery inhibit and delay minor low- auxin production sites inside the lamina; which therefore affect the developmental timing of vein hierarchy formation. Thus, the first vessels to differentiate are the primary ones (**Figure 1A**) that build the basic vascular network, originating from the lobs. Among them are the delicate veins that connect the inner lamina tissues, which develop later and will connect the already differentiated primary vascular bundles in an organized and orderly pattern characterized by plasticity and continuity.[1]

## 6. The control of vessel width along the plant body by hormonal gradients

The flow of water along plants is crucially affected by vessel width[2], which also affects xylem pathology and adaptation.[12,19] Therefore, it is important to understand the mechanisms that control the diameter and density of these vascular conduits.

There is a general pattern of increasing vessel width and decreasing vessel density from leaves to roots, where vessels are narrow near the auxin producing young leaves and wide near the roots.[1,2] Knowing that vessels are directly induced by IAA, the documented polar gradient pattern of vessel width and vessels density raises the questions: what is the long-distance auxin signaling mechanism that controls vessel width and density along the plant axis? If this mechanism is based on decreasing IAA concentrations from leaves to roots, it raises additional basic question:

what is the evidence for a decreasing gradient of auxin concentration along the plant axis from leaves to roots? or does IAA act as a morphogen[20,21], which stimulates its own degradation (by conjugation and catabolism) along its downward polar transport to induce gradients, or is it a self-enhancing signal that promotes its transport[11] and thus forms gradients, which provides positional information to the cells through which it flows?

Morphogen gradients were suggested as mechanisms for assigning positional information within a field. Accordingly, models explaining how positional information is set up and how it is interpreted by developing cells were proposed for different patterns and biological systems in both animals and plants.[20,21, 22]

In vascular differentiation, the polar transport of the bioactive auxin is the morphogenetic signal that is suggested to create such a gradual polar gradient in the vascular cambium (embryonic tissue along the plant) providing directional and location information to the differentiating cells along the morphogenetic field. To explain the mechanism that controls the gradual patterns of increasing vessel size and decreasing vessel density from leaves to roots, Aloni and Zimmermann[23] proposed the following *auxin gradient hypothesis* (that was first named the *six-point hypothesis*):

The hypothesis proposes that the final diameter of a vessel is determined by the rate of cell differentiation. Since cell expansion ceases after a limiting developmental event (in developing vessels of plants: the deposition of the secondary wall), high- auxin concentrations near the young leaves induce narrow vessels, because of their rapid differentiation, allowing only limited time for cell widening. Conversely, further away from the auxin producing leaves, low-auxin concentrations result in slow differentiation, which permits more cell expansion before secondary wall deposition and therefore results in wide vessels at the base of the stem.

Vessel density is controlled by, and positively correlates with IAA concentration; consequently high-auxin concentrations (near the IAA producing young leaves) induce great vessel density, while low-auxin concentrations (further down, towards the roots) diminish density. Consequently, vessel density decreases from leaves to roots.

The auxin gradient hypothesis was experimentally confirmed by showing that various auxin concentrations applied to decapitated stems induce substantial gradients of increasing vessel diameter and decreasing vessel density from the auxin source towards the roots. High-auxin concentrations yielded numerous vessels that remained narrow because of their rapid differentiation; low-auxin concentrations resulted in slow differentiation and therefore in fewer and wider vessels.[1,23]

It is suggested that similar signal gradients likely regulate polar patterns of increasing blood-vessel width along the human body, with increasing distance from the sites that produce the signal. For example, during vasculogensis in developing embryo hands, it is likely that the blood-vessel signal, possibly VEGF, likely produced at the fingertips, creates a gradient of decreasing signal from the fingertips towards the heart, which induces fast blood-vessel differentiation at the fingers, resulting in early development of narrow blood vessels at the fingertips. While slower blood-vessel differentiation further away from the fingertips, result in wider blood vessels.

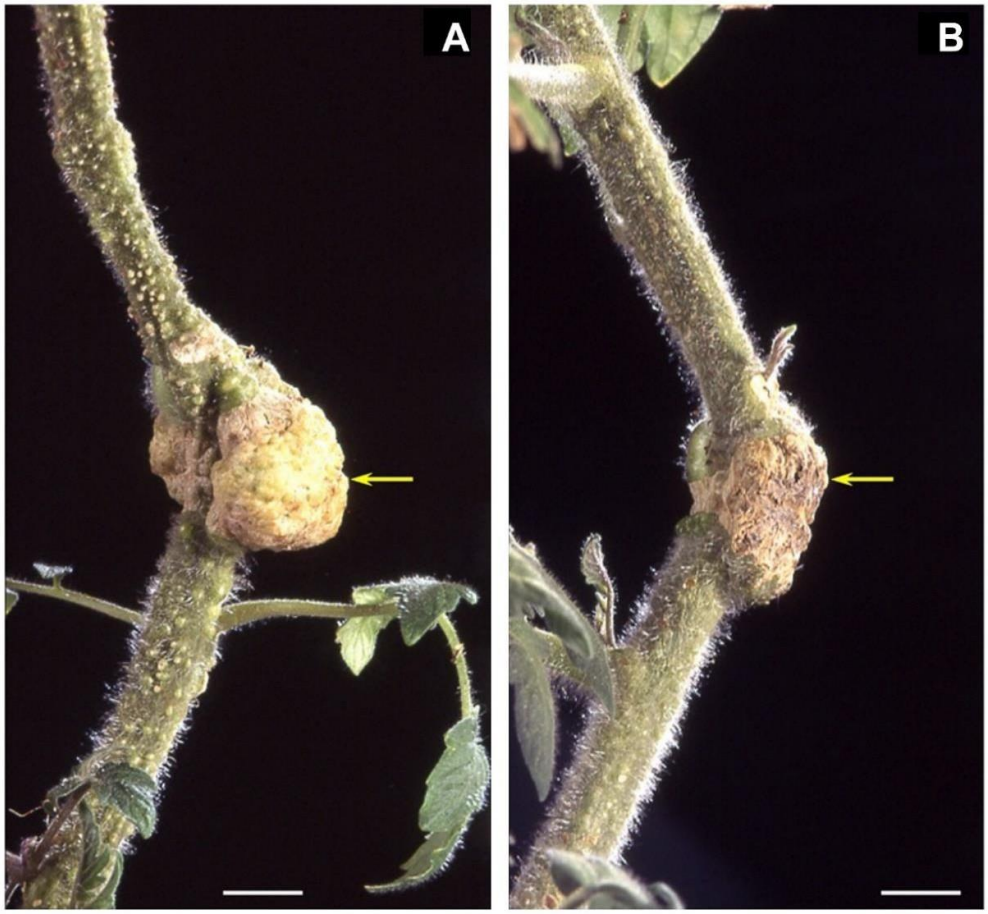
## 7. Cancer and vascular differentiation

### 7.1 Role of vascular differentiation in plant tumor development

A holobiont is a host organism in interaction with all associated microorganisms as an entity for selection in evolution.[24] Plants and humans are holobionts, namely, they are host organisms that are in interaction with bacteria that may promote their performance, or cause health problems.

Plants might develop cancer.[1,25] Most of the studies show that the development of cancer in plants is associated with infection of bacteria. This phenomenon raises the question of whether cancer in humans is also linked to infectious bacteria? The latest discovery that different types of human cancers are also associated with specific infecting bacteria,[26] will likely open new strategies for cancer therapy in humans, and will be discussed below.

**Figure 2:** Influence of ethylene insensitivity on cancer development




2-month-old *Agrobacterium tumefaciens*-induced crown-gall tumors (*marked by yellow arrows*) on tomato (*Lycopersicon esculentum*) stems. Both tumors were induced by applying the *A. tumefaciens* bacteria to wounds made on the stems. On a normal (wild type) tomato, the cancer limited stem width and shoot growth above the tumor (A), in comparison to retarded cancer development on the ethylene-insensitive *Never ripe* mutant, while stem width and shoot growth continued normally above the tumor (B); demonstrating typical side views of a cancerous gall on a wild-type stem (A), compared with a restricted growth of a fibrous hard tumor on the ethylene-insensitive stem (B). Bars = 10 mm, from[41]

In plants, wounding followed by infection of the soil bacterium Agrobacterium tumefaciens, induces tumors (**Figure 2A**). Young infected plants might not survive and die. However, plant cancers do not ultimately kill their host, but reduce plant growth and can cause damage to crop yield of agricultural plants, by reducing the quality and quantity of fruits, which may cause severe economic damages.

Therefore, understanding the control mechanisms of tumor development is a basic tool and a major request for finding cure solutions and preventing cancer damages in plants. In addition, understanding the hormonal and bacteria role in developing plant tumors has the potential of inventing therapy solutions to cure also cancers of human beings.

The most studied and common tumor in plant, which can infect and develop on hundreds of different sensitive dicotyledonous species, is called crown gall, which is induced by the soil bacteria *Agrobacterium tumefaciens* and *A. vitis*.[27,28] The vectors which transfer the bacteria to plants are usually insects, which wound the plant and infect the injured tissues. The bacteria do not induce crown gall tumors without wounding. Cellular changes are required in dividing plant cells at the wound in order to generate cancer. The important discovery that from a large *Agrobacterium tumefaciens* tumor inducing plasmid, namely, *Ti-plasmid*, a DNA sequence of about 20 kb, *T-DNA*, is stably incorporated into the higher plant genome[29,30] was a break- through in molecular

biology and biotechnology. The T-DNA-located oncogenes have been identified. The most prominent ones which induced the tumor are those encoding enzymes of auxin (*iaaM*, *iaaH)*, cytokinin (*ipt*) and opine biosynthesis (*nos*/*ocs*).[31] Opine is used by the infecting bacteria as a specific source of their nutrient supply.

Different bacteria are known to induce cancer in plants. The different cancer- inducing bacteria express the oncogenes *iaaM* and *iaaH* for auxin synthesis, which induces high levels of IAA in developing tumor galls. These oncogenic genes were found in *Pseudomonas syringae*, which causes gall tumors on olive and oleander[28], and in *Erwinia herbicola pv*. *Gypsophilae,* which induces tumorous galls in *Gypsophila*.[32] Likewise, the cytokinin synthesis pathway via isopentenyltransferase (*ipt*) has been found in microorganisms. However, in *Agrobacterium tumefaciens* galls,[33] after infection and the T-DNA is stably incorporated into the higher plant genome, there is no need for the presence of the *A. tumefaciens* bacteria in the gall for its additional production of the auxin and cytokinin hormones that induce cancer development. But galls induced by other bacteria require the presence of the bacteria that continue to produce high concentrations of auxin and cytokinin.

The integration and expression of the T-DNA of the bacterial Ti plasmid within the plant nuclear DNA[34] substantially elevate auxin concentrations in crown gall tissues, which may be 500 times higher in the tumor than in control tissues.[35]

Based on the three-dimensional-pattern analysis of vascular tissues in tumors and the restriction of vessel development in host tissues, Aloni et al.[19] proposed that the high auxin levels, which are known to enhance ethylene synthesis,[36,37] promote the synthesis of ethylene in crown galls. Nevertheless, there are no specific oncogenes for ethylene synthesis in the bacterial T-DNA. It is also possible that elevated cytokinin levels, which may be 1500 times higher in the tumor than in control tissues[35,38] might also promote ethylene synthesis, because cytokinin is also known to stimulate ethylene production.[39,40] In addition, it is possible that there is a synergistic effect within crown-gall tissues whereby a combination of the elevated levels of both auxin and cytokinin boosts ethylene production in the tumor.

Aloni et al. [41] and Wächter et al.[42] showed that tumor-induced ethylene is a limiting and controlling factor of crown gall morphogenesis. High-ethylene concentrations were produced continuously by growing crown galls during a few weeks in tomato,[41] up to 140 times more ethylene than in wounded, but not infected control stems of *Ricinus communis* reaching a maximum at five weeks after infection.[42]

The ethylene effect of tumors, which reduces vessel diameter in the host stem adjacent to the cancer and above it, demonstrate that in addition to the well-defined roles of auxin and cytokinin, there is a critical role for the gaseous hormone ethylene in determining crown-gall morphogenesis. The continuous production of normal wide vessels in the stem of the ethylene-insensitive plants[41] ensures water-supply priority to the ethylene-insensitive host shoot over the tumor, while limiting water supply and nutrients to the initiating crown gall tumors, reduces (**Figure 2B**), or even inhibits cancer development. Evidently, the use of ethylene-insensitive agricultural plants prevents tumor development, and even if there is an infection, cancer growth is limited[41] and does not reduce plant growth, fruit quality and quantity on infected plants. The selection for ethylene insensitive or low-ethylene sensitivity fruit trees, which are usually tumor free, is the simplest and most effective method for solving the severe economic damage induced by the most devastating and common cancer on wild-type plants. In modern agriculture, lines of insensitive-ethylene fruit plants are being used and should be practice worldwide for preventing cancer damages in crop plants for obtaining high agricultural yields.

### 7.2. The involvement of bacteria in cancer development in human beings and antibiotic applications

Interestingly, also at the mitochondrial level and strict dependence on mitochondrial biogenesis, Lamb et al.[43] found that mitochondrially-targeted antibiotics are efficient in eradicating cancer stem cells (CSCs), across many tumor types under *in vitro* experimental conditions. The study demonstrated that 4-to-5 different classes of FDA-approved antibiotics (azithromycin, doxycycline, tigecycline, pyrvinium pamoate, and the anti-parasitic drug chloramphenicol) can be used to selectively target CSCs, across several tumor types, in 12 different cancer cell lines, across 8 different tumor types (breast, ductal carcinoma in situ, ovarian, prostate, lung, pancreatic, melanoma, and glioblastoma

(brain)). Lamb et al.[43] findings imply the possible involvement of bacteria in human tumor development, similar to cancer- inducing bacteria in plants; suggesting that mitochondrial-targeted antibiotics should also be considered for prevention studies specifically focused on the prevention of tumor recurrence and distant metastasis. Additionally, early clinical trials with the doxycycline and azithromycin antibiotics (intended to target cancer-associated infections, but not cancer cells) have already shown positive therapeutic effects in cancer patients, although their ability to eradicate cancer stem cells was not yet appreciated.[43]

The recent analysis of Nejman et al.[26] on tumor microbiome, from 1526 tumors and their adjacent normal tissues across seven cancer types, including breast, lung, ovary, pancreas, melanoma, bone, and brain tumors, revealed that each tumor type has a distinct microbiome composition. Breast cancer had a particularly rich and diverse microbiome. It was further found and visualized that the intratumor bacteria are mostly intracellular and are present in both cancer and immune cells.[26] The bacteria enhance cancer cell fitness by protecting the cancer cells from the immune system.[44,45] Consequently, antibiotic treatments that will eradicate the bacteria from the immune system will expose the unprotected cancer cells to the bacterium-free immune cells.

The potential microbiome impacts on cancer biology require more research, for better understanding the role of bacteria in human cancer, which will enable new strategies and therapeutic approaches for cancer patients.[45,46]

### 7.3. The plant hormone jasmonate is a promising candidate for human cancer therapy

Jasmonate was recorded in early stages of crown-gall tumor formation.[47] The naturally occurring plant hormones Jasmonates, including their volatile methyl jasmonate (MeJA), which activate defense-related genes against insects and pathogens,[48,49] induces cell cycle arrest, apoptosis and non-apoptotic cell death selectively in animal cancer cells; therefore, are promising candidate to the cure of human cancer.[50] Jasmonate induced swelling of mitochondria isolated from cancer cells but not from normal ones. Thus, the selectivity of jasmonates against cancer cells is rooted at the mitochondrial level, and probably exploits differences between mitochondria from normal *versus* cancer cells.[51]

Several research groups have reported in recent years that members of the plant defense hormone family of jasmonates, and some of their synthetic derivatives, exhibit anti-cancer activity *in vitro* and *in vivo*. Jasmonates increased the life span of EL-4 lymphoma-bearing mice, and exhibited selective cytotoxicity towards cancer cells while sparing normal blood lymphocytes, even when the latter were part of a mixed population of leukemic and normal cells drawn from the blood of chronic lymphocytic leukemia (CLL) patients.[52]

Thus, Jasmonates join a growing number of old and new cancer chemotherapeutic compounds of bioactive plant originating secondary metabolites.[28] Hence, the jasmonate family is a promising novel anti-cancer agent that present new hope for the development of cancer therapeutics, which should attract further scientific and pharmaceutical interest.[28,52,53]

### 7.4. Bioactive secondary metabolites

The exploitation of bioactive secondary metabolites originating in plants to treat human cancer has a tremendous therapeutic potential. Various isolated phytochemicals and their synthetic derivative extract from plants may offer new therapy options to decrease human tumor incidence and mortality (Ullrich et al. 2019).

## 8. Concluding remarks

This review exposes physicians and medical researchers to hormonal mechanisms that induce and regulate vessel formation in plants, providing tools and ideas for understanding blood-vessel differentiation in the human body, specifically during vasculogensis in developing embryos. Basic issues as vascular continuity, unpredictable patterns of vessel formation, and gradients in vessel diameter are discussed in plants, hoping to promote similar research in human beings.

Like in plants, cancer development in humans is associated with bacteria. More research is needed to clarify the role of bacteria in cancer development and how to develop advance treatments to cure human tumors. The bacterium-cancer recent findings support a promising concept for cancer therapy of combining antibiotics with other human cancer therapeutic treatments for increasing the recovery success from cancer. Generally, the use of generic antibiotics for anti-cancer therapy should significantly reduce the costs of patient care, making treatment more accessible, especially in developing countries.

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