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Review

Molecular mechanisms linking environmental toxicants to cancer development: Significance for protective interventions with polyphenols

Ricardo Lagoa [a,b,*], Dorinda Marques-da-Silva [a,b], Mário Diniz [b,c], Maria Daglia [d,e], Anupam Bishayee [f]

[a] School of Technology and Management, Polytechnic Institute of Leiria, Morro do Lena, Alto do Vieiro, 2411-901 Leiria, Portugal
[b] Applied Molecular Biosciences Unit, NOVA School of Science and Technology, NOVA University of Lisbon, 2829-516 Caparica, Portugal
[c] Department of Chemistry, NOVA School of Science and Technology, NOVA University of Lisbon, 2829-516 Caparica, Portugal
[d] Department of Pharmacy, University of Naples Federico II, 80131 Naples, Italy
[e] International Research Center for Food Nutrition and Safety, Jiangsu University, Zhenjiang 212013, China
[f] Lake Erie College of Osteopathic Medicine, 5000 Lakewood Ranch Boulevard, Bradenton, FL 34211, USA

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ABSTRACT

Human exposure to environmental toxicants with diverse mechanisms of action is a growing concern. In addition to well-recognized carcinogens, various chemicals in environmental and occupational settings have been suggested to impact health, increasing susceptibility to cancer by inducing genetic and epigenetic changes. Accordingly, in this review, we have discussed recent insights into the pathological mechanisms of these chemicals, namely their effects on cell redox and calcium homeostasis, mitochondria and inflammatory signaling, with a focus on the possible implications for multi-stage carcinogenesis and its reversal by polyphenols. Plant-derived polyphenols, such as epigallocatechin-gallate, resveratrol, curcumin and anthocyanins reduce the incidence of cancer and can be useful nutraceuticals for alleviating the detrimental outcomes of harmful pollutants. However, development of therapies based on polyphenol administration requires further studies to validate the biological efficacy, identifying effective doses, mode of action and new delivery forms. Innovative microphysiological testing models are presented and specific proposals for future trials are given. Merging the current knowledge of multifactorial actions of specific polyphenols and chief environmental toxicants, this work aims to potentiate the delivery of phytochemical-based protective treatments to individuals at high-risk due to environmental exposure.

1. Introduction

Environmental exposure to organic and metal toxicants is an important driver of carcinogenesis. In addition to well-established carcinogens, low-dose exposures to several environmental chemicals that are not individually carcinogenic may instigate and/or enable carcinogenesis (the low-dose carcinogenesis hypothesis) [1–3]. Epidemiological evidence for this association has been difficult to consolidate, but many experimental studies show that several compounds including polycyclic aromatic hydrocarbons, pesticides and heavy metals, trigger cellular and molecular alterations that can ease cancer development.

Critically important for researchers, policy-makers and general public, the conventional approaches consisting of single-chemical-as-carcinogen risk assessment, exposure avoidance and strict environmental regulations may not be effective to protect populations from chronic low-dose exposures to harmful toxicants and mixtures [2,4]. In other front against environmental drivers of disease risk, authors just called for new strategies to address the deleterious effects of metabolism-disrupting chemicals and the growth of metabolic diseases across the globe [5]. Recognizing that multiple exposures to procarcinogenic agents through the lifetime, even in discontinuous and veiled ways, may contribute to cancer and chronic diseases, adds value to potential protective interventions.

Previous reviews have discussed the biological potential of specific herbs or natural compounds to alleviate the effects of harmful environmental exposures [6,7], but the present work aims to empower a multidisciplinary audience better able to set up novel bioproducts and future trials successfully. Discussed below, mechanistic evidence,

* Corresponding author at: School of Technology and Management, Polytechnic Institute of Leiria, Morro do Lena, Alto do Vieiro, 2411-901 Leiria, Portugal.
E-mail address: ricardo.lagoa@ipleiria.pt (R. Lagoa).

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epidemiological data and some clinical trials already available give credit to the ability of certain polyphenols to counteract toxicities of priority environmental chemicals associated to carcinogenesis, paving the way for nutraceuticals targeting harsh environment-related risks.

2. Environmental concerns and search for nutraceuticals

Human exposure to environmental toxic agents showing diverse mechanisms of action is an increasing concern under climate and environmental change scenarios. Epidemiological studies have estimated that approximately 80 % of all cancers are related to environmental factors. Individual cancer susceptibility can be the result of several host factors, including differences in metabolism, DNA repair, altered expression of tumor suppressor genes and proto-oncogenes, and nutritional status. In fact, xenobiotic metabolism is the principal mechanism for maintaining homeostasis during the body's exposure to xenobiotics [8]. As will be discussed in the following sections, diverse environmental chemicals can trigger genotoxic and non-genotoxic mechanisms considered to play major roles in carcinogenesis. However, a totally supported classification of human carcinogens is demanding and for many harmful environmental chemicals it is not possible to establish a safe level [4].

Lee and Jacobs reasoned that the traditional chemical-focused approach to human protection, typically recommendations to avoid sources of exposure and stricter environmental regulations, do not work for prevention of low-dose toxicity of pollutants [4]. These authors called for a human-based approach combining experimental integrative studies and further epidemiological analysis in research, monitoring chronic environmental exposures and early effects of chemical mixtures, and adopting lifestyles such as exercise and diet to control pollutants' toxicokinetics and attenuate their effects.

The analysis of organochlorine pesticides, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and polycyclic aromatic hydrocarbons (PAHs) in 121 Romanian subjects detected p,p′-dichlorodiphenyldichloroethylene (DDE), β-hexachlorocyclohexane (HCH), PCB-153, phenanthrene and naphthalene in blood samples from more than one third of the participants, some toxicants in median concentrations higher than one μ-g/L [9]. In a larger study carried out in the urban area of Tehran (Iran), urinary levels of hydroxyl-PAH were found related to traffic and diverse lifestyle factors [10]. Also in Tehran, health risk assessment of ambient fine particulate matter (PM) using the WHO AirQ + model estimated an annual mortality of 27 cases of lung cancer [11].

Air pollution is one of the leading causes of deaths in Southeast Asian countries including India [12]. A risk assessment of the PAHs in dust of Beijing attributed a major contribution of ambient dust particles to the cancer risk in "daily-life" urban environments, and identified benzo(a) pyrene (B[a]P) and dibenzo(a,h)anthracene as predominant compounds with higher risk of inducing carcinogenicity [13].

Exposure to toxic pollutants during critical developmental periods (e.g. prenatal, infancy) is especially worrying [4,14]. Exposure to pesticides, heavy metals and industrial chemicals are problematic for numerous children at different parts of the globe [15,16]. A report on seven countries from South and southeast Asia has indicated that outdoor and household air pollution is the more common environmental health problem for children, and whose solutions are not immediately apparent or easily implementable [16].

The developing fetus is highly vulnerable to effects of toxicants. For instance, exposure to arsenic in the uterus induced alterations in DNA methylation in the newborn liver that were related to cancer development later in life [14]. Infants born to mothers exposed to arsenic showed increased expression of inflammatory and DNA damage markers and the follow-up of these children indicated impairment of oxidative DNA repair [16,17].

In a study with pre- and peri-pubertal girls (6–8 years old), high detection rate (95 %) of urine hydroxyl-PAHs was observed in association with tobacco smoke exposure and consumption of grilled food [18]. Exposure to environmental tobacco smoke at home and gas-based appliances used to cook or heating water also resulted in higher levels of fluorene and phenanthrene metabolites measured in the urine of 3-year-old children at Krakow, Poland [19].

Moreover, the total body burden of some environmental chemicals, such as organochlorine pesticides, increases with age, putting older people at higher risks [9]. Other risk groups are occupationally exposed individuals. For example, cooks are exposed to particles, mutagenic aldehydes, naphthalene and other PAHs [20]. A recent study measured higher urinary levels of benzene, toluene, ethylbenzene and xylenes (BTEX) in professionals of composting facilities after the work shift, and personal protective equipment seems not preventing exposure [21]. Workers exposed to insecticides have also been a growing concern, both field operators and at production industries, showing for example high blood concentrations of chlorpyrifos-methyl and endosulfan, in correlation to aminotransferases levels and DNA damage [22].

Facing the exposure to these increasingly more common environmental toxicants, and not disregarding the importance of controlling exposure settings, which depends on public health and individual avoidance measures, there is a need for effective approaches to attenuate or ideally eliminate their harmful effects.

Healthy exercise and dietary lifestyles are suggested as means to decrease body burden of toxicants by promoting their excretion from the body, and to mitigate early harmful impacts in cells by the activation of resistance mechanisms [4]. With potential, different mild stress-inducing behaviors, from exercise to nutritional patterns, may stimulate cellular innate defenses and repair systems by activation of (xeno)hormetic mechanisms [4,23].

Nutritional status is well-accepted to modify toxicants impact in human health [6,14], but direct evidence of the beneficial efficacy of specific diets, nutrients or dietary components is difficult to establish due to the complex interactions between inter-individual variability and numerous environmental factors. Nevertheless, empiric or ethnopharmacological knowledge about the utility of some plants has been corroborated by different *in vivo* and *in vitro* data identifying botanical preparations and active ingredients that modify absorption or excretion of dangerous chemicals, or alleviate their biochemical toxicity.

Plant-derived polyphenols are a diverse collection of bioactive compounds, including flavonoids, hydroxycinnamic acids and stilbenes, widely distributed in the human diet. In the search for nutraceuticals and bioformulations preventing deleterious effects of environmental factors in human health, a wide range of evidence point to polyphenols as a plausible choice. Founding *in vivo* experiments showed that black and green tea, including aqueous extract and decaffeinated, inhibited skin carcinogenesis induced by UV and 7,12-dimethylbenz[a]anthracene (DMBA) in mice [24]. A multifactorial chemopreventive capacity was also early established for resveratrol, the chief stilbene present in grapes and wine [25].

Mounting experimental data and anti-carcinogenesis molecular actions of polyphenols will be discussed after, but epidemiological evidence also gives important support for the preventive role of representative compounds. Flavonoid intake was associated with reduced risk of breast [26] and colorectal cancer [27]. Inverse relations were also reported between different flavonoid classes and several cancers, namely, oral, laryngeal, esophageal, colorectal, breast, ovarian and renal, but not with prostate cancer [28]. In a different study, lower prostate cancer risk was associated to higher intake of quercetin [29], similarly to lung cancer risk [30]. In a recent large work, a 24 % lower risk of head and neck (oral, pharyngeal and laryngeal) cancers was found for the highest quintile of total flavonoid intake, with stronger association to anthocyanidins class, but no role detected in esophageal and gastric cancers [31]. Regarding tea consumption, dose-response meta-analyses have been consolidating the association with decreased incidence of cancer types as the oral [32,33]. The biological activities of green tea have been attributed to the catechin polyphenols in its

composition, being epigallocatechin-3-gallate (EGCG) the major constituent with important anti-carcinogenesis molecular actions.

3. New perspectives on the contribution of environmental exposures to carcinogenesis

3.1. Environmental carcinogens

Table 1 presents environmental chemicals for which there is strong epidemiologic evidence of a causal association between human exposure and cancer, and thus classified as carcinogenic to humans by the Environmental Protection Agency of United States (EPA), and by the International Agency for Research on Cancer (IARC) [34–38]. Additionally, more than 60 agents are considered by EPA as likely to be carcinogenic to humans, based on data of carcinogenicity in animal testing and limited evidences from human studies, but without the strong epidemiologic or mechanistic association requested for full classification as human carcinogen. Among these agents, several priority pollutants can be found, such as the heavy metal cadmium, polychlorinated biphenyls (PCBs), the organophosphate insecticide dichlorvos, and the organochlorine insecticides aldrin, dichlorodiphenyltrichloroethane (DDT), dieldrin and pentachlorophenol. Cadmium and several dioxin-like PCBs (PCB 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189) are carcinogenic to humans according to IARC.

Table 1
Environmental chemicals classified as carcinogenic to humans and tumor caused according to the guidelines of Environmental Protection Agency of United States [34–37] [a].

Chemical	Tumor Type	Environmental occurrence (including occupational exposition)
Arsenic, inorganic	Skin cancer and lung cancer	Air, drinking water, diet, smoking, diverse industrial environments
Asbestos (Libby Amphibole)	Lung cancer and mesothelioma	Air, drinking water, mining and milling of asbestos, manufacturing or use of products containing asbestos
Benzene	Leukemia	Cigarette smoke, air contaminated with benzene, drinking water, diet, solvents, some industrial environments
Benzidine	Bladder tumors	Consumer goods containing benzidine, benzidine based-dyes, exposition to benzidine
Benzo[a]pyrene (B[a]P)	Forestomach, esophagus, tongue, and larynx tumors, squamous cell neoplasia in the larynx, pharynx, trachea and nasal cavity	Drinking water, cigarette smoke, air, water, soils, food, pharmaceutical products, diverse industrial environments
Beryllium and compounds containing beryllium	Lung cancer	Beryllium dust, fumes from the burning of coal, fuel oil, cigarette smoke, drinking water, diet, natural occurrence in soils, mines
Bis(chloromethyl) ether (BCME)	Respiratory tract tumors	Direct inhalation, dermal contact with vapours
1,3-Butadiene	Leukemia	Fires, cigarette smoke, vehicle emissions, some industrial environments
Chromium (VI)	Lung cancer	Air, drinking water, diet, treated wood, chromium wastes, some industrial environments
Coke oven emissions	Respiratory cancer	Industrial environments
Ethylene oxide	Lymphoid cancer and breast cancer	Cigarette smoke, some industrial, hospital environments
Nickel (refinery dust, subsulfide)	Lung cancer	Contaminated air, diet, cigarette smoke, everyday items containing nickel, some industrial environments
Trichloroethylene	Renal cell carcinoma, non-Hodgkin's lymphoma and liver tumors	Diet, drinking water, certain industrial environments
Vinyl chloride	Liver angiosarcoma, angiomas, hepatomas, hepatocellular carcinoma and neoplastic nodules	Air, drinking water, diet, cigarettes smoke, dermal contact with consumer products, some industrial environments

[a] These environmental chemicals were also classified as human carcinogens by the International Agency for Research on Cancer [38,42].

Multiple data show relevant associations between cancer incidence and exposure to various environmental toxicants, most notably heavy metals and pesticides [39,40]. Exposure to metals, including arsenic (As), cadmium (Cd), hexavalent chromium (Cr(VI)) and nickel (Ni), induce cell transformation and have been linked to different types of cancer in humans [39,41]. In fact, As, Cr(VI) and Ni are currently classified as carcinogenic to humans by both IARC and EPA [34–36,42].

B[a]P causes gastrointestinal and head and neck (airway) cancers (Table 1), and it is an example of a 'complete' carcinogen, i.e. a substance that can cause cancer on its own with recognized effects on the different steps of carcinogenesis [43]. The genotoxicity and carcinogenicity of B[a]P is attributed to benzo(a)pyrene-7,8-diol-9,10-epoxide (B[a]PDE), the highly electrophilic metabolite known to form DNA adducts (Fig. 1). Nevertheless, a chemical may not be carcinogenic on its own, but it may contribute to carcinogenesis in the presence of other disruptive agents [1] and, eventually, favored by some specific genetic background. With this in mind, progress in the characterization of the carcinogenic potential of chemicals pursues biological information of the targets and pathways affected by low-doses and/or environmentally-relevant mixtures [1,44,45]. Goodson et al. [1] reviewed the biological data of many non-carcinogenic chemicals known to exert effects at low doses related to cancer hallmarks, and found evidence of pro-carcinogenic cross-hallmark effects with several ones, including 2,2-bis-(p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE), atrazine, bisphenol A, copper, cypermethrin, DDT, dichlorvos, lindane, malathion, nickel chloride, and different phthalates.

3.2. Complexity of the carcinogenic processes related to environmental exposures

Considering the multistep nature of carcinogenesis, it is reasonable to accept that complementary exposures may act in concert to cause cancer by means not predictable from the carcinogenicity of individual chemicals. Importantly, combinations of disruptive exposures are expected to synergize if acting in key mechanisms/pathways related to different cancer hallmarks [1]. Moreover, pro-carcinogenic exposures to different contributing agents may occur sequentially or discontinuously, and not necessarily in simultaneous or in continuous way. Using a zebrafish model, Martins et al. [45] showed how oncogene Ras expression and neoplasia-related inflammation marks persisted after short-term exposure to cadmium and B[a]P, in spite of the low oxidative and genetic toxicity, and even after toxicants withdrawal.

The network of effects and interactions between different chemicals in human exposome affecting varied physiological processes diverges from the classic reductionist views of one chemical-one target [44]. Analysis of causal relations in these complex settings is still a challenge [40], but advances in toxicology from multi-level (molecular to environmental) and systems biology approaches have been refining carcinogen classes, dose-response relationships and toxicity mechanisms especially relevant for chronic illness [46–48].

While the genotoxicity of (single) chemicals keeps being extensively probed, other phenomena are increasingly established as contributing to

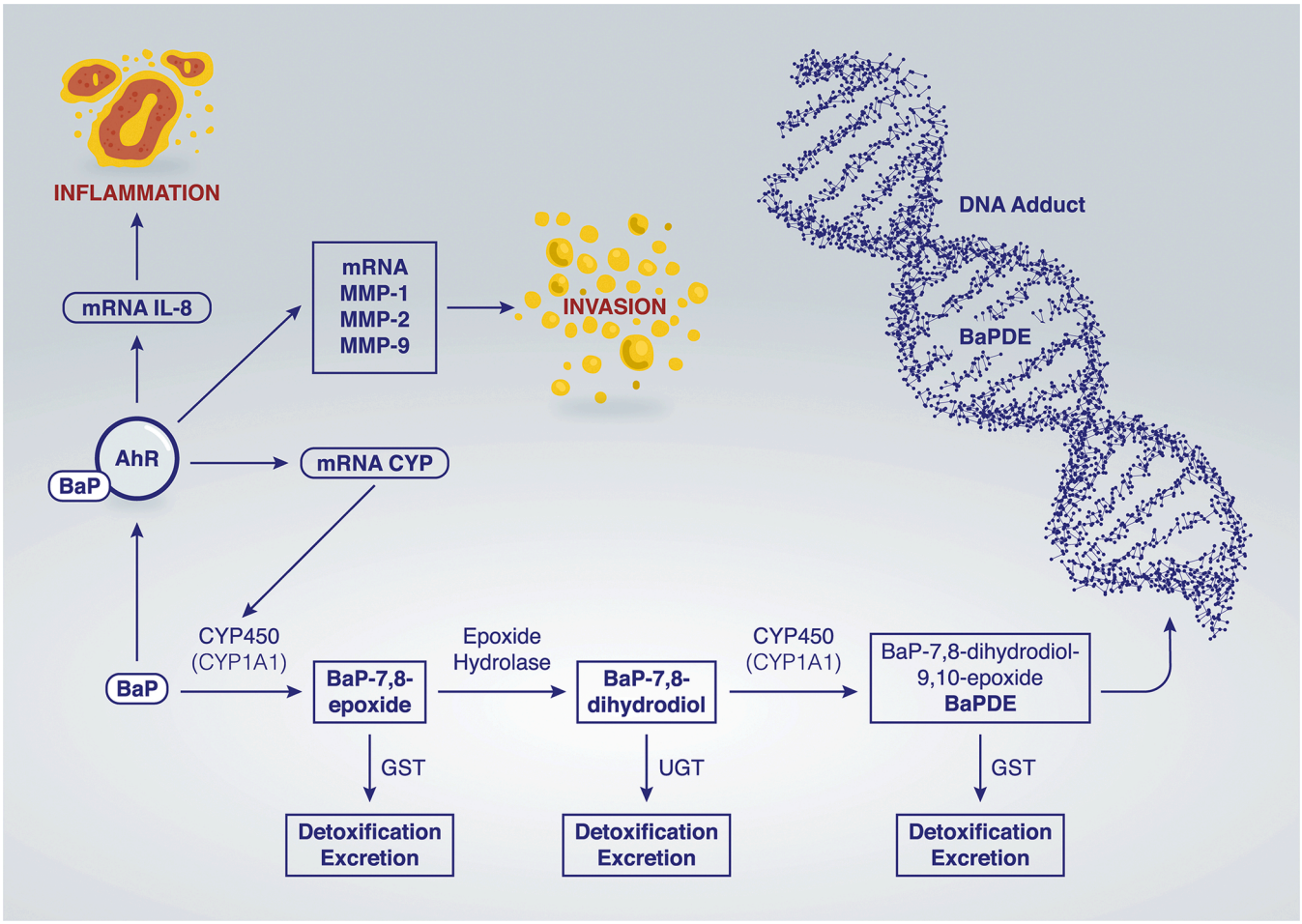

Fig. 1. The carcinogenicity of benzo[a]pyrene (B[a]P) is associated to its genotoxic potential and non-genotoxic mechanisms contributing for cancer development. Metabolism of B[a]P by cytochrome P450 enzymes (CYP450), mainly the CYP1A1 type, and by epoxide hydrolase produces benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide (B[a]PDE), an electrophilic agent that forms DNA adducts. Detoxification enzymes glutathione S-transferases (GST) and uridine diphosphate-glucuronyltransferase (UGT) neutralize and promote excretion of B[a]P dangerous metabolites. B[a]P also activates the aryl hydrocarbon receptor (AhR) that induces the expression of CYP450 enzymes and other genes, namely, the inflammation-related interleukin (IL)-8 and invasion-related matrix metalloproteinases (MMP).

carcinogenesis or mutagenesis, namely inflammation, infections, endocrine disruption, epigenetic changes, immune dysfunction or redox imbalance [12,39,40,44,49–51] (Fig. 2). Therefore, different environmental toxicants or factors can act with cooperation of a vulnerable genome and primed epigenome to cause malignant transformations [40].

Toxic mixtures are present in outdoor air pollution, outdoor air PM and diesel exhaust particles that were all considered human carcinogens by IARC, causing lung cancer and showing positive associations with bladder cancer [52,53]. Øvrevik et al. [44] discussed previously the multiplicity of cellular effects triggered by combustion exhaust particles with regard to cancer initiation, underscoring the pro-inflammatory processes. Besides organic compounds as PAHs, air PM can contain significant levels of iron, vanadium and other metals, penetrate mucus, accumulate in cytosol, mitochondria and vesicles of pulmonary cells, generate reactive oxygen species (ROS) and induce the release of inflammation- and cancer-related interleukins (IL) [54–57].

In occupational environments specific carcinogens are known and their effects may be isolated in some cases, but the carcinogenic potential of mixtures or low exposures doses is more difficult to follow. Assuming there is no threshold dose, environmental toxicants may favor cancer development by altering the DNA, disturbing cell repair and detoxification mechanisms, impairing effective immune surveillance and deregulating inflammation [14,40,57–59].

3.3. *Detoxification roles in carcinogenesis*

Detoxification processes are complex, have high individual variability and are influenced by the environment, lifestyle and genetic heritage of the individual [60]. Therefore, the role of detoxification pathways in cancer development and prevention calls for a specific attention [14]. Usually, xenobiotics metabolization occurs in two reaction phases: phase I generally followed by phase II. The phase I system mainly involves oxidation reactions, mostly through the cytochrome P450 (CYP), but other reactions may also occur (e.g., hydrolysis, reduction). Phase II comprises conjugation reactions catalyzed by enzymes (transferases). Toxicant metabolism and conjugation can produce chemical forms less toxic and/or more prone to renal excretion, so full activity of these biochemical pathways in the corresponding organs is critical for toxicant's elimination (Fig. 1). Regarding metal toxicants, metallothioneins must be remembered for their functions in metal homeostasis and renal excretion, but also for other roles in cell cycle regulation, antioxidant defense and its increased expression in some types of cancer [61].

The cytochromes P450 metabolize many compounds, including environmental carcinogens, toxins and numerous anticancer drugs, and have an important role in tumor formation but also in their treatment. In fact, numerous pre-carcinogens are activated by the CYPs and they are also involved in the activation and inactivation of anticancer drugs [62].

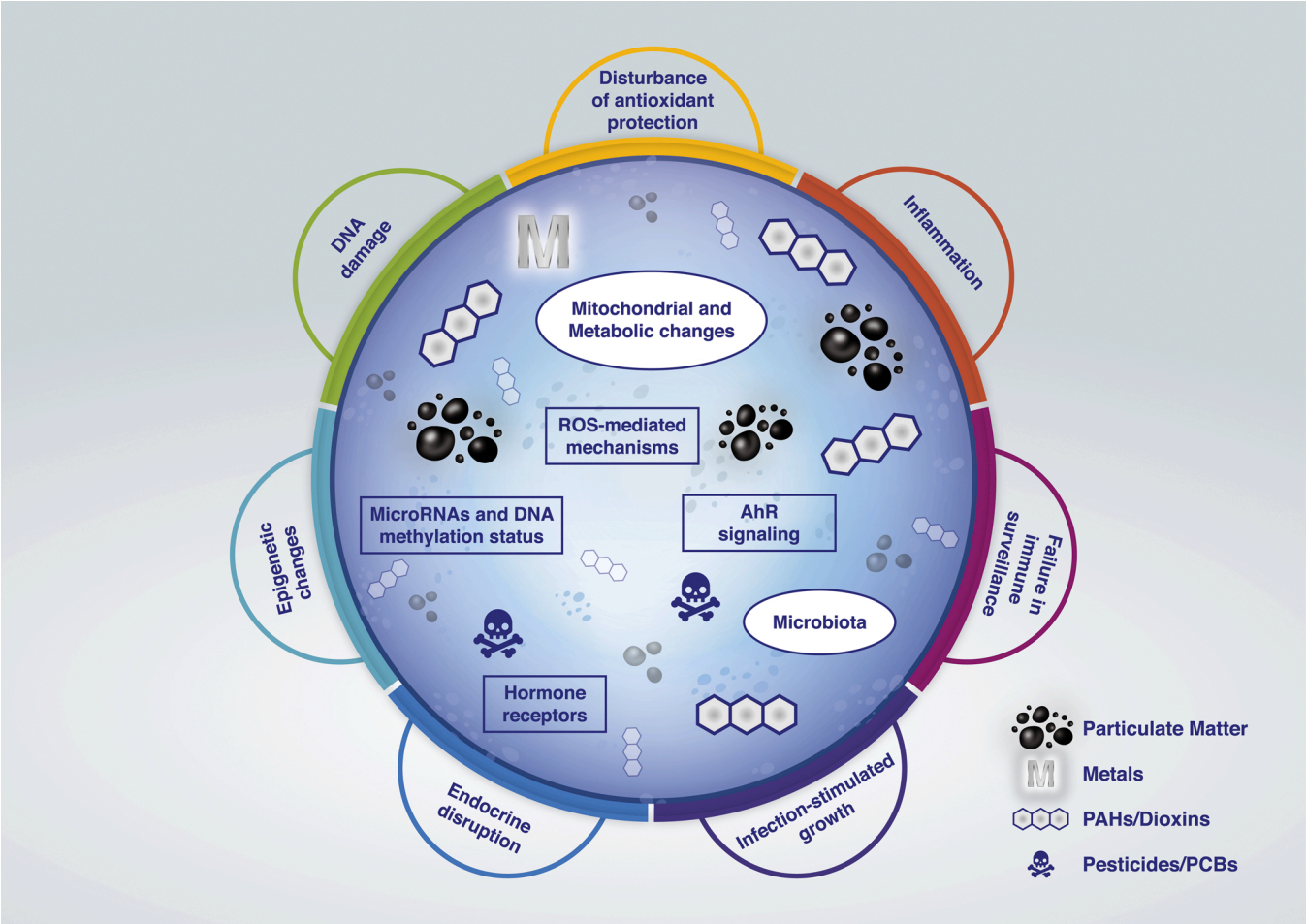

Fig. 2. Cellular and molecular changes prompting carcinogenesis associated to environmental exposures. Different biological alterations induced by isolated or mixtures of environmental toxicants are known to favor the development of cancer. Abbreviations: AhR, aryl hydrocarbon receptor; PAHs, polycyclic aromatic hydrocarbons; PCBs, polychlorinated biphenyls; ROS, reactive oxygen species.

For instance, phase I metabolism via CYP enzymes also activates some chemicals to more potent carcinogens, as in the illustrative case of B[a]P shown in Fig. 1 [63,64]. Moreover, CYPs expression was observed in various types of cancers (e.g. breast, colon, lung, ovarian), with CYPB1 being identified as the main CYP1 produced in several tumors [65–67]. Moreover, Dhaini et al. [68] showed high levels of CYP3A4/5, in primary osteosarcoma, which metabolize the anticancer drugs used to treat this cancer and was suggested that this CYP may have a major role in chemotherapy resistance of osteosarcomas. Although many anticancer drugs are inactivated by CYPs metabolic action, other prodrugs are activated by CYP action, making them cytotoxic and thus efficient in fighting cancer. For example, CYPB1, involved in steroid hormones metabolization, has a key role in susceptibility to cancers as breast and prostate cancers which are known to be hormone-dependent. CYP2A6 metabolizes pre-carcinogens from tobacco, anticancer drugs (e.g. tegafur) and drugs with clinical relevance as nicotine, coumarin, halothane, among others [69].

Proper nutrition is also an important factor to secure vitamins for detoxification pathways, and vitamin C and E are traditionally regarded [55,70]. High doses of these vitamins are necessary to achieve anticancer effects [71], and these facts are more established in the case of pharmacological vitamin C that is able to trigger hydrogen peroxide production and mitochondrial dysfunction in cancer cells [72,73]. At low (steady-state) intracellular concentration, vitamin C protects cells by acting as an antioxidant capable of neutralizing ROS and preserving mitochondrial functions as well as cofactor for different redox enzymes [55,71,73]. It has been shown in rats that vitamin C and E (α-tocopherol) prevented arsenic-induced lipid peroxidation, as well as the decrease in reduced glutathione (GSH) levels and in mitochondrial enzyme activities [74]. A mitochondria targeted vitamin E analog was reported to inhibit mitochondrial transcription in cancer cells but not in normal tissue [75]. Nevertheless, results from clinical interventions with these antioxidant vitamins have been limited [76]. Alternatively, polyphenols can inhibit the oxidation of α-tocopherol and augmented the vitamin concentration in rat blood and liver after diet fortification [77].

3.4. Classic players and new molecular mechanisms in environmental carcinogenesis

Certain persistent organic pollutants (POPs) as PCBs, dioxins and DDT are legacy contaminants, i.e. have their production terminated or greatly limited, but persist in the environment at very relevant levels for a long time to come. PAHs and flame retardants are other important examples of POPs. Carcinogenic PAHs and dioxins can be found in vehicle exhaust, air PM, particulates from coal combustion, cigarette smoke, and in foods [59].

Dioxins and dioxin-like POPs, such as polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and (planar) PCBs, interact with aryl hydrocarbon receptor (AhR), which triggers a “dioxin-like” response mechanism [78–83]. PAHs are foremost ligands of AhR which is also a key target of combustion exhaust particles [84]. Non-dioxin-like POPs can interact with binding sites for hormones, behaving as endocrine disruptors, or elicit other toxic mechanisms. The transcription factor AhR binds a broad range of xenobiotics and upon

activation upregulates xenobiotic-metabolizing enzymes, such as the cytochrome P450 family gene CYP1A1 that produces ROS, leading to oxidative stress and inflammation in different organs [44,78,85]. Additionally, in the case of B[a]P, the cytochrome P450-mediated metabolism enables the formation of DNA adducts [63], an essential mechanism in cancer initiation (Fig. 1). Therefore, the inhibition of AhR activation and P450 enzyme inhibition afforded by diverse polyphenols is recognized an important anticancer activity [86,87]. Different groups reported that quercetin and tea polyphenols suppress DMBA-induced hamster buccal pouch carcinomas, by downregulation of CYP1A1 and CYP1B1 expression, inhibition of oxidative stress and pro-inflammatory signaling, while the methoxyflavonoid chrysoeriol prevented B[a]P binding to AhR and formation of DNA adducts [85,86]. However, the chemopreventive actions are not restricted to inhibition of phase I metabolism/activation of procarcinogens, since for example black raspberry reduces DNA damage, mutagenesis and oral tumors caused directly by B[a]PDE [88]. Very recently, the reduction of B[a]P-induced colon tumors by resveratrol was associated with diminished phase I metabolism (metabolic activation) of B[a]P, upregulation of phase II metabolism by glutathione S-transferase (GST, detoxification), and decreased concentrations of B[a]P-DNA adducts in colon and liver [64].

Endocrine disruptors generally interfere with estrogen, androgen and thyroid hormonal control mechanisms in different tissues, and have been associated with reproductive and neurodevelopmental toxicities. Non-coplanar PCBs, PBDEs, bisphenol A, phthalates, DDT and other organochlorine pesticides, can act as estrogen receptor agonists or antagonists, exert antiandrogenic activity and/or target the thyroid system [49,89–91]. In addition to nuclear receptors-mediated actions, rapid effects of some endocrine disruptors on intracellular calcium or cAMP levels implicate membrane receptors such as G protein-coupled receptors (GPCRs) in the toxicity mechanisms [92].

Environmental carcinogenicity driven by genotoxic mode of action is completely recognized, but recent research is substantiating the causal role of epigenetic changes in the development of clinically relevant cancers. For example, hexavalent chromium [Cr(VI)] increases histone-lysine methyltransferases in close association with malignant phenotypes of transformed cells [39]. Cr(VI) compounds are confirmed human carcinogens for lung cancer (Table 1). A cross-study comparison of genomic/epigenomic changes induced by Cr(VI) in lung identified the enrichment of cytotoxicity/cell proliferation pathway and general suppression of genes involved in DNA damage repair, predicted to be modulated by epigenetic regulators [93].

Inherent and/or toxicant-induced compromise of DNA repair capacity seems a key mechanism for predisposition to cancer [46]. DNA repair pathways include base excision repair, nucleotide excision repair, mismatch repair and homologous recombination among others [46,94]. A previous study on occupational exposure to mercury found no direct genotoxic changes, but a significant deficiency in DNA base excision repair capacity in the workers [58]. Exposure to Cr(VI) decreased the expression of mutL homolog1 (MLH1) and RAD51 recombinase in cellular models and in workers involved in production of chromate materials for several years [93,95]. MLH1 is a tumor suppressor gene participating in DNA mismatch repair and RAD51 has an important role in homologous recombination. Decreased expression of more genes implicated in DNA damage response was reported in human lung cells *in vitro* and, interestingly, the changes were partially alleviated by pre-treatment with EGCG [95]. It should be noted that different polyphenols can modulate the DNA repair machineries in response to DNA damaging agents and conditions related to cancer [94].

In addition to reducing the level of the protein Rad51, Cr(VI) caused its mislocalization to the cytoplasm, suppressing homologous recombination repair important to maintain high genomic fidelity [96]. Phthalates can also reduce the expression of genes involved in homologous recombination (e.g. breast cancer gene 1, BRCA1), as well as in mismatch (MutS homolog, MSH, genes) and nucleotide excision (e.g. proliferating cell nuclear antigen, PCNA) repair pathways [97]. Reinforcing the role of DNA repair deficiencies in carcinogenesis, repeated Cr(VI) exposure was demonstrated to cause permanent and heritable phenotypes of impaired repair, amplified centrosomes and chromosome instability [98]. Moreover, concomitant exposure to other toxicants that affect DNA repair efficiency can contribute to carcinogenesis risk [99].

It was recently observed in electroplating workers exposed to chromium higher levels of DNA oxidative damage, measured as 8-oxo-2'-deoxyguanosine (8-OHdG), and decreased mRNA expression of the repair enzyme 8-oxoguanine DNA glycosylase 1 (OGG1) [100]. OGG1 is critical in the DNA base excision repair pathway by recognizing oxidized guanine bases, but its activity is compromised in conditions of oxidative stress and, surprisingly, can modulate nuclear factor-kappa B (NF-κB) signaling and induce inflammation [101].

4. Merging recent findings in action mechanisms of environmental toxicants and anticancer polyphenols

Although polyphenols and other phytochemicals are ancient treatments for many diseases, their mode of action is still not perfectly clear. Initially connected with free radical scavenging and antioxidant actions, current research indicates polyphenols trigger more elaborate protective mechanisms at cellular and molecular levels, which may be paramount for preventing environmental toxicant-induced carcinogenesis.

4.1. Cell redox signaling

Environmental carcinogens are in general oxidative *per se* or induce the production of free radicals and reactive oxygen species (ROS) in cells, leading to DNA modifications, mutations and carcinogenesis. Hence, the free radical scavenging abilities of polyphenol antioxidants was a straightforward justification of their cancer preventive effects.

Typical anticancer polyphenols were consistently demonstrated to counteract oxidative stress and DNA damage elicited by carcinogens; illustrative examples are quercetin and silymarin (milk thistle, *Silybum marianum*) against *in vitro* and *in vivo* arsenic exposure [14,102,103], quercetin and tea polyphenols prevention of DMBA-induced oxidative DNA damage [85,86], or tea polyphenols reduction of PM-induced lipid oxidation in human alveolar epithelial A549 cells [104] and in plasma of PCB-126 exposed mice [105]. PCB-126 is considered the more toxic dioxin-like PCB by its productive AhR binding [82].

Olive oil phenolics as hydroxytyrosol prevented DNA damage by peroxynitrite [106], and by the epoxides of styrene and 1,3-butadiene in human peripheral blood mononuclear cells [107]. Low concentrations in olive-derived extracts also prevented the genotoxicity (comet assay) of heterocyclic amines [108]. In a valuable chemopreventive model, oleuropein reduced azoxymethane-induced DNA damage in peripheral leukocytes, colon preneoplastic lesions, severity of crypt dysplasia and incidence of medial colon tumors in mice [109].

However, *in vivo* scavenging of radicals by low doses of exogenous antioxidants is probably ineffective, and flavonoid's prevention of ROS formation may be more effective by the inhibition of key enzymatic systems that generate oxidants in the cells. PM and B[a]P-enhanced generation of ROS in different cells was related to mitochondrial changes and (AhR-dependent) induction of NADPH oxidase systems [55,56,79,110]. Quercetin, kaempferol, delphinidin, hesperetin, naringenin, ferulic acid, cyanidin, certain catechins and metabolites were found to inhibit mitochondrial generation of ROS and membrane NAD(P)H oxidase activities in normal and transformed cells [55,110–115]. Diverse polyphenols are also inhibitors of superoxide-producing cytochrome P450 enzymes, showing effective concentrations in sub-micromolar range [86,105]. Depending on the subcellular accumulation of the polyphenols, namely at mitochondria [116], these inhibitory properties may control dangerous sources and the distribution of superoxide anion, hydrogen peroxide, hydroxyl and lipid free radicals at critical cellular locations. Moreover, redox modulation of proteins at crossroads of cell

signaling processes can further extend the reach of bioactive polyphenols [117,118].

Maintenance of the nucleophilic tone and para-hormesis, i.e. the paradoxic oxidative induction of cellular antioxidant response mechanisms, is argued more significant than free radical scavenging capacities to understand the beneficial actions of antioxidants [119]. The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is a remarkable intrinsic antioxidant mechanism and the ability of polyphenols to activate Nrf2 should be underlined for their potential role in modifying toxicants' consequences [6,23,120]. Nrf2 is a key transcription factor that modulates the expression of several antioxidant enzymes, such as NAD(P)H:quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), catalase, glutathione peroxidase, GST and heme oxygenase-1 (HO-1), among several others that protect cells against oxidative stress and xenobiotics [23,121]. Moreover, Nrf2 interacts with AhR signaling, as the promoter region for Nrf2 contains AhR-binding regions and the gene promoter for AhR contains Nrf2-binding elements [122].

Therefore, it is highly relevant that many dietary polyphenols generally activate Nrf2 pathway, notably resveratrol, tea catechins, luteolin, curcumin, protocatechuic and tannic acids [83,120,123–127]. Epicatechin (and an *in vivo* metabolite) protected skin fibroblasts from UV radiation, an effect associated to increased expression of HO-1 and abolished by a protein synthesis inhibitor [128]. DNA binding and transcriptional activity of Nrf2 was increased by curcumin in rat, and by EGCG in human mammary epithelial cells, whilst oral soy isoflavone formulation modulated the expression of a range of Nrf2-dependent genes in mice prostate [120]. Green tea increased the expression of NQO1, SOD1 and GST in the liver of animals treated with PCB-126 [105], while kaempferol upregulated Nrf2 in the brain of chlorpyrifos-exposed rats [129]. DJ-1 (PARK7) is a multi-functional protein assisting the expression of Nrf2-associated antioxidant enzymes, and protocatechuic acid and EGCG were reported as strong inducers of DJ-1 and HO-1 protein expression, as well as being able to attenuate induced oxidative lesions in gastrointestinal mucosa of rats [130].

Formulations containing tea polyphenols, epicatechin, proanthocyanidins and quercetin sustained antioxidant defenses, and counteracted ROS production and oxidative stress caused by lead, mercury and PCBs in animal models [105,131–134]. Looking mechanistically, EGCG and quercetin inhibit dioxin and PCBs-induced cellular oxidative stress, by decreasing ROS formation, modulating AhR and NF-κB mechanisms, and upregulating Nrf2-related antioxidant genes [78,80,81,83,135].

It is plausible that direct targeting of redox proteins and ROS-producing enzymes by polyphenols, and/or stimulation of intrinsic Nrf2-dependent defenses, contribute in different conditions to prevent escalating of oxidative stress driven by environmental toxicants, and ensuing genotoxicity and inflammation. Different levels of cellular or sub-cellular oxidative stress trigger distinct redox-sensitive transcription factors and put forward different biological responses. Low levels of oxidants activate Nrf2, and polyphenols in these conditions maintain physiological nontoxic concentrations of nonradical oxidant electrophiles important to instill cellular antioxidant enzymes and repair systems [119,136]. Overwhelming oxidative stress will cause cell death, whereas moderate levels of ROS can trigger an inflammatory response mediated by activator protein-1 (AP-1) and NF-κB, the first known redox-regulated transcription factor [127,136]. NF-κB signaling in carcinogenesis and its modulation by polyphenols will be further discussed in the section devoted to inflammation.

Recently, the transcription Kruppel-like factor 9 and associated ROS signaling was implicated in melanocytic premalignant growth [137]. Cancer cells generally have an upregulated antioxidant system to support ROS levels [138,139], and apoptosis resistance of cancer stem-like cells was associated to low ROS release, while increased generation of ROS favored apoptosis and inhibition of tumorigenesis [41]. In accordance, potent cancer therapy with polyphenols seems mostly supported by the prooxidant action of the compounds able to generate cytotoxic oxidative stress and fight tumors [127,140], but cancer prevention is associated to the antioxidant and anti-inflammatory properties [25,120,124–126,141]. In this regard, Nrf2 activation has been pointed detrimental for cancer therapy, because genetic studies on some cancers suggest a possible oncogenic nature of constitutive Nrf2 activation as cause of resistance to chemotherapy [50]. Therefore, the apparent contradictory dual role of Nrf2 in cancer needs to be rationalized in the context of the experimental models used, and constitutive activation should be distinguished from nucleophilic tone-induced regulation [142]. In an interesting study, Son et al. [126] observed that luteolin activates inducible Nrf2 and decreases Cr(VI)-induced ROS in normal bronchial epithelial cells, but Nrf2 is constitutively activated in the metal-transformed cells and, in this case, the flavonoid inhibits Nrf2 activation. *in vivo*, a gallotannin-rich extract from *Caesalpinia spinosa* returned contrasting effects on tumor growth in mice when treatment was administered prophylactically or only therapeutically [143].

Ha et al. [111] reported the chemopreventive action of syringic acid by reduction of UV-induced skin tumorigenesis in mice. *in vitro*, the polyphenol inhibited NADPH oxidase activity and ROS production by human epidermal keratinocyte HaCaT cells irradiated by UV, as well as AP-1 transactivation, cyclooxygenase (COX)-2 and matrix metalloproteinases (MMP)-1 expression [111]. Similar antioxidant and inhibition of the Mitogen Activated Protein Kinases (MAPKs) signaling pathway was previously described by Lim et al. [112] for delphinidin in UV-irradiated human dermal fibroblasts. Airborne PM also induce production of ROS by human bronchial epithelial cells and oxidative stress in mice lung tissues, with a pro-inflammatory response mediated by NF-κB signaling [51,55]. PM causes mitochondrial dysfunction and the generation of ROS sets off redox signaling mechanisms associated also to epigenetic alterations [12,56]. All these indications for the triggering role of oxidative stress in environmental toxicant-induced mechanisms reinforce the importance of the different antioxidant molecular actions of polyphenols.

4.2. Cell calcium homeostasis

Calcium signaling is one of the major regulated processes in cell physiology. Deregulation of cytosolic Ca^{2+} was previously reported after *in vivo* exposure to pesticides and as early event of their toxicity *in vitro* [144,145], and the role of calcium control mechanisms in cancer pathogenesis is gaining increasing attention. Traditionally connected to ROS and receptor signaling pathways, cellular calcium mechanisms are pointed as a possible target in cancer [146,147].

The store-operated calcium entry (SOCE) process is central for calcium signaling in non-excitable cells [148], and has been found to be altered in cancer cells (Fig. 3). Activation of GPCRs results in Ca^{2+} release from endoplasmic reticulum (ER) via the inositol 1,4,5-trisphosphate (IP_3) signaling pathway and, following this ER calcium depletion through IP3 receptors, the SOCE is activated to gradually replenish cellular calcium levels [149]. Two proteins are key players in the SOCE mechanism: STIM1 and Orai1. At the ER membrane, STIM1 acts as a sensor for calcium. When Ca^{2+} levels are low it couples to Orai1, a highly sensitive Ca^{2+} channel located in the plasma membrane allowing Ca^{2+} entry into the cell (Fig. 3A).

Various studies have been pointing GPCRs, such as adrenergic and dopaminergic receptors, as targets of environmental toxicants mediating their immune and metabolic effects, and B[a]P was demonstrated to bind to the beta2-adrenergic receptor [92,150]. Orai1 and STIM1 expression are increased in cancer cells, namely in malignant esophageal squamous cell carcinoma [151], in multiple myeloma cells [152] and in cervical cancer [153]. In addition, pharmacologic inhibition, or reduced expression or silencing of Orai1 and STIM1 suppressed proliferation of cervical cancer cells [153], and migration of esophageal squamous cell carcinoma KYSE-30 [151], decreased breast tumor metastasis in animal models [154] and induced apoptosis in multiple myeloma [152]. Moreover, the remodeling of channel-forming ORAI subunits is also

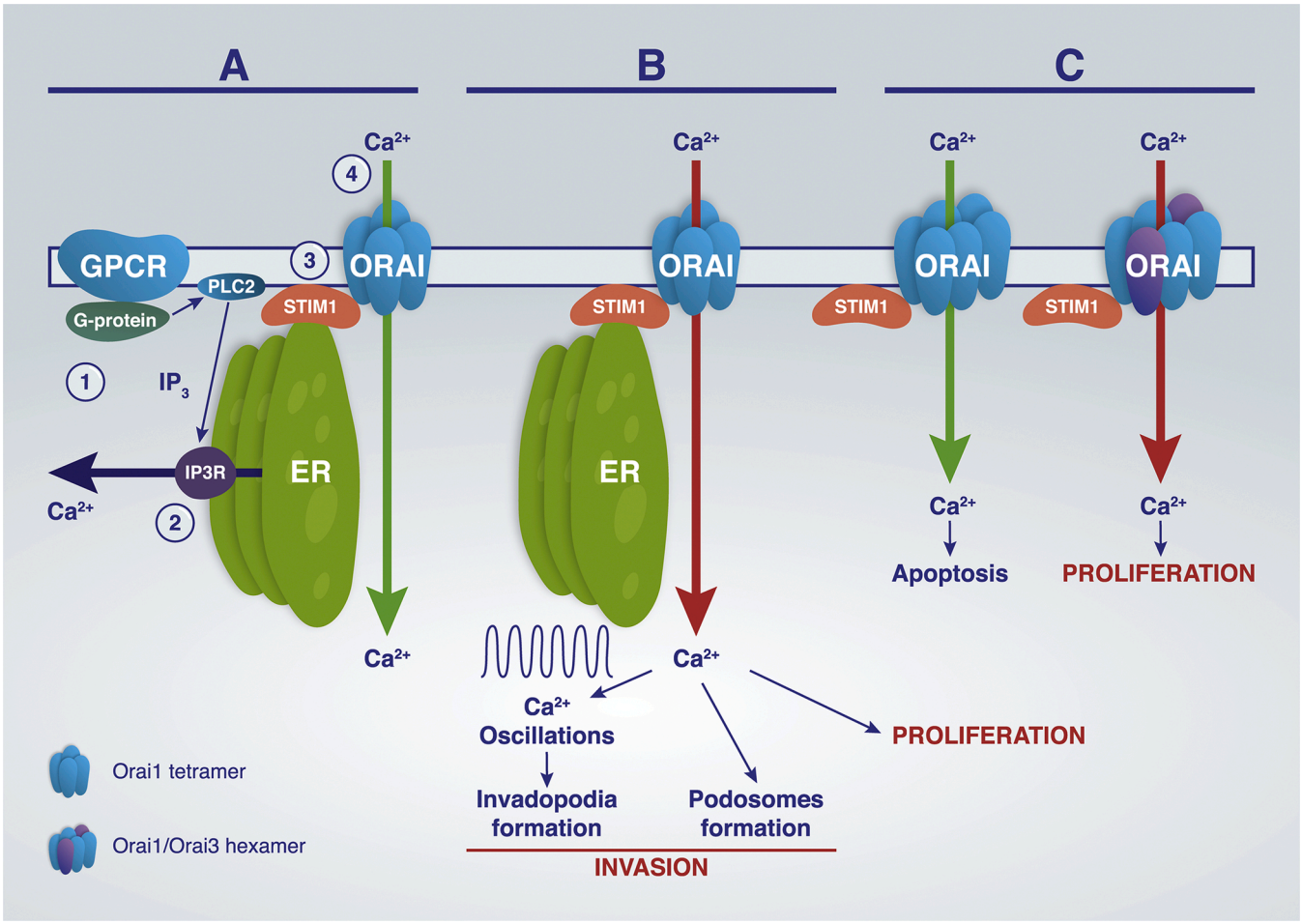

Fig. 3. Store-operated calcium entry (SOCE) in cancer cells. Panel A: Activation of G protein-coupled receptors (GPCRs) and phospholipase C (PLC) triggers the IP3 signaling pathway ; IP3 causes endoplasmic reticulum (ER) Ca^{2+} depletion via IP3 Receptors ②; Stromal interaction molecule (STIM)-1 acts as a sensor for ER Ca^{2+} levels and couples to Calcium Release-Activated Calcium Modulator (Orai)-1 at the plasma membrane ③; Orai-1 channel opening and Ca^{2+} entry ④. Panel B: Altered SOCE-mediated Ca^{2+} entry in cancer cells causes proliferation and formation of invasion structures. Panel C: Remodeling of Orai channel modifies calcium regulation as a switch mechanism between apoptosis and proliferation.

described as determinant in prostate cancer [155]. In these conditions, the channel was proposed as a hexamer. However, the channel presents different selectivity for calcium depending on its tetramer or hexamer conformation [156,157] (Fig. 3B and C). Analyzing the ratio of Orai1/Orai3 channel-forming proteins, it was shown that Orai3 determines the oncogenic switch between two Ca^{2+} channel phenotypes: arachidonic acid-regulated and store-operated. The first phenotype is associated to a ratio of 1:3 for channel-forming ORAI proteins (Orai1: Orai3), being relevant for proliferation, and the second phenotype represented by a ratio of 1:1 was more associated to apoptosis [155] (Fig. 3C).

Additionally, there is a differential redox sensitivity of ORAI channel-forming proteins. Orai1 but not Orai3 presents an extracellular reactive cysteine that when oxidized by H_2O_2 causes inhibition of the channel [158]. In fact, the response of Orai1 to ROS in prostate cancer cells induces alterations in Ca^{2+} signaling via SOCE channels contributing to higher susceptibility to ROS-induced cell death [159].

Calcium signaling regulates proliferation and increased number of cell cycles at different checkpoints and via Ca^{2+}/calmodulin complex [160]. During cell cycle, it is known that SOCE activity is upregulated in G1/S transition and downregulated from S to G2/M transition [161]. STIM1 silencing inhibits cell proliferation in cervical cancer, gliobastoma, hypopharyngeal carcinoma and in head and neck squamous cell carcinoma [153,162–164] by arresting the cell cycle at the G0/G1 phase [162,163] or at the S and G2/M phases [153].

Concerning migration, adhesion and invasion, Mo and Yang discussed the role of SOCE and ensuing activation of calmodulin and calpain in metastasis and colonization mediated by actin cytoskeleton reorganization [165]. Inhibition of SOCE and STIM1 impaired cell migration and invasion by regulating focal adhesion turnover in hepato-carcinoma cells [166]. Focal adhesion turnover is an invasion process in which extracellular matrix proteolytic remodeling occurs to overcome tissue barriers. Two different membrane protrusions actin-rich structures are described to mediate focal degradation of the extracellular matrix – invadopodia and podosomes [167,168]. SOCE was found to be necessary to orchestrate the formation of these structures [169,170]. In more detail, the assembly and activity of invadopodium was regulated by spatiotemporal organization of calcium oscillations derived from calcium entry via SOCE, namely STIM1/Orai1 in melanoma cells [169]. In the case of podosomes formation, STIM1-mediated Ca^{2+} signaling plays a crucial role in podosome-mediated cell invasion observed in transformed mouse embryonic fibroblasts breast cancer MDA-MB-231 cells and osteosarcoma U2OS cells [170] (Fig. 3B).

Recently, pyrene was described to induce an increase of intracellular calcium in human microvascular endothelial cells and human embryonic kidney cells. This PAH compound provokes Ca^{2+} release from intracellular stores and a subsequent extracellular Ca^{2+} influx equivalent to SOCE [171]. Remarkably, this pyrene-induced Ca^{2+} increase was dependent on AhR activity, while in other work B[a]P increased

cytosolic calcium by activation of adrenergic receptor [150]. In human macrophages, B[a]P induced a rapid and transient increase of cellular calcium, and production of the chemokine CCL1 was blocked by inhibiting the calcium increase with a chelator or with a SOCE inhibitor [172]. In addition, AhR genomic signaling triggered by dioxin was found to be controlled by the calcium/calmodulin-dependent protein kinase (CaMK) pathway [173]. Very recently, organic chemicals extracted from diesel exhaust particles increased calcium concentration in endothelial cells via AhR non-genomic signaling, and via adrenergic receptors and protease activated receptor 2, these both GPCRs [174,175]. Moreover, the transformation of human bronchial epithelial cells to a malignant phenotype by B[a]P presented increased expression of STIM1 when compared to human bronchial epithelial cells. In line with this, mice lung tissues treated with B[a]P also presented higher expression of STIM1 when compared to control tissue [176].

The ability of polyphenols to modulate calcium signaling in cancer cells and changes induced by environmental carcinogens is an open field for research. Resveratrol was described to decrease STIM1 expression, as well as Ca^{2+} entry via SOCE, leading to ER stress and autophagic cell death in prostate cancer cells [177]. In other cell line, resveratrol was also shown to decrease SOCE via inhibition of ERK1/2 activation and STIM1 phosphorylation [178]. Ji et al. [147] implicated the IP_3 receptors in cytosolic Ca^{2+} accumulation and ER stress induced by stemphol, which caused mitochondrial swelling and permeability transition pore opening, and ultimately the death of leukemia cells.

4.3. Metabolic remodeling and mitochondria

Reprograming of cellular bioenergetics and metabolism is an emerging mark of cancer with implications for multiple other processes, including redox and calcium homeostasis, DNA repair and proliferation signaling [179]. Glucose metabolism in cancer cells relies mostly on aerobic glycolysis (Warburg effect), oxidative phosphorylation may be slowed down and energy significantly generated from lactic fermentation, while high glucose uptake promotes anabolic and reducing power-generating pentose phosphate pathway in the cytosol [3,180,181].

Robey et al. [3] defended that pro-carcinogenic not directly genotoxic exposures may act through molecular mechanisms involving cellular metabolism. In accordance, nanomolar concentrations of B[a]P inhibited the respiration of hepatic epithelial cells and increased lactate levels, prompting the appearance of a mesenchymal-like phenotype [182]. In rat lungs, PM reduced the ATP level, the activity of enzymes of the tricarboxylic acid cycle and the expression of mitochondrial respiration chain proteins, and promoted the glycolysis by increasing the expression and activity of hexokinase and pyruvate kinase [183]. PM-induced decrease in ATP production may be related to mitochondrial dysfunction and the lower energetic efficiency of glycolysis [180,184]. Upstream cellular redox or calcium deregulation can be a cause for mitochondrial permeability transition, impairment of the electron transport chain, metabolic disruption or other mitochondrial complications [80,136,185].

Diverse environmental toxicants have been described to damage mitochondria [186,187]. In the case of PM, alterations to the mitochondrial morphology were previously reported by other authors [55]. Dioxin also caused the loss of mitochondrial activity and integrity *in vitro* [80,188]. More recently, Tremblay-Laganière et al. [187] related the oxidative stress induced by PCB-126 in rat tissues to the respiratory inhibition measured with complex I substrates, while Hu et al. [185] showed how low concentrations of cadmium in drinking water cause mitochondrial protein oxidation and deregulate fatty acids and lipid metabolism in mouse lung. Noteworthy, metabolome markers of PCB oxidative stress and mitochondrial dysfunction were amplified in mice with a pre-existing liver injury [189]. In humans, a just published analysis of endogenous metabolites in 397 maternal perinatal serum samples found profiles of lipids and acyl-carnitine intermediates associated with a DDE derivative of DDT, indicating mitochondrial impairment in those women [190].

It is not clear if the metabolic and mitochondrial changes caused by environmental carcinogens play a primary role, but toxicant-induced mitochondrial dysfunction likely contribute for a pro-oncogenic state, and metabolic shifts seem a prerequisite for both cancer genesis and progression [3]. Prostate cancer prevention in a mouse model was recently associated with downregulation of fatty acid metabolism [191]. In a study of Cr(VI)-transformed human bronchial epithelial cells, forced expression of fructose-1,6-bisphosphatase (glyconeogenesis enzyme) in cancer stem-like cells promoted ROS and apoptosis, inhibiting tumorigenesis [41]. Thus, strategies to avoid mitochondrial and metabolic deregulation may afford chemopreventive potential.

Concerning mitochondrial effects, and beyond the redox regulation discussed previously, quercetin has been the polyphenol more systematically characterized [192]. Quercetin can regulate the activity of mitochondrial complex I and initiate a change of the HepG2 cell glycolytic phenotype [115,193]. It also showed protective actions against PM damage to mitochondrial structure and function [55]. Nevertheless, other studies point to additional polyphenols as apigenin and silibinin having mitochondrial targets mediating their anticancer activities [138,194]. Martino et al. [80] investigated the cellular calcium deregulation and mitochondrial depolarization triggered by dioxin, and reported the preventive action of EGCG. Omidian et al. [110] measured an increase in MitoSOX Red (mitochondrial superoxide) signal induced by B[a]P in fibroblasts similar to the induced by antimycin A, a respiratory electron chain blocker, and cyanidin was the more potent inhibitor in that conditions.

Dioxin-like PCBs down-regulated the rate-limiting gluconeogenic gene phosphoenolpyruvate carboxykinase in hepatocytes, in parallel with their ability to activate AhR, reversed by the flavonoid myricetin [82]. Cumulatively, PCB-126 decreased hepatic expression of glucose-6-phosphatase in mice [195]. It should be mentioned that the Warburg effect is also implicated in cancer-linked inflammatory processes [196], and Cardenas et al. [197] related the anti-inflammatory actions of apigenin in mice lung to the flavonoid's ability to preserve mitochondrial function.

4.4. Epigenetics and non-coding RNAs

An expanding body of evidence support the influence of signaling mechanisms regulated by DNA methylation, histone modifications and non-coding RNAs (e.g. microRNAs) in carcinogenesis [39,93,198], and epigenetic remodeling is likely to play a major role in environmental toxicants low-exposure and transgenerational effects [12,14,40]. The higher degree of epigenetic plasticity of stem/progenitor cells, concurrently with their differentiation and regeneration capacity, may increase the vulnerability of these cells to environmental factors and position them for malignant transformation [39,40].

The role of epigenetic changes in carcinogenesis can be further highlighted in the case of metal carcinogens arsenic, cadmium and nickel, which are weakly mutagenic and do not display strong genotoxicity [39,45]. Various epigenetic changes prompted by hexavalent chromium seem closely connected to alterations in cell proliferation and DNA damage repair capacity, leading to genomic instability and tumorigenesis [93]. Hypermethylation of MLH1 and RAD51 genes was detected after Cr(VI) exposure, causing decreased expression of the corresponding proteins involved in DNA repair, including in samples from occupationally exposed workers [93]. Modulation of DNA methylation maintenance proteins, as the DNA methyltransferases, seems to underlie the changes in methylation patterning at the MLH1 promoter region [93]. Exposure to PM and PAHs has also been associated with changes in DNA methylation with most studies pointing to decreased methylation [12,199]. It must be taken into account that ROS oxidize 5-methylcytosine, favoring DNA demethylation [199]. Oxidative stress can also inhibit the functions of DNA methyltransferases and

the one-carbon metabolism that provides the methyl groups [12,199]. In other example, phthalates were demonstrated to reduce expression of the DNA methyltransferase 1 [97]. With adult volunteers, exposure to diesel exhaust induced demethylation of promoter regions of genes in the MAPK and NF-κB pathways [200]. Global decreases in DNA methylation were observed on exposure to air PM [201], but different studies on air pollution show substantial variability and the specificity, possible concentration-dependent effects and time variation still require more investigation [12,199]. Various investigators noticed important changes in the DNA methylome caused by metals, such as nickel, arsenic, cadmium, and chromium (VI), and also by DDT, dioxins, perfluorooctanesulfonic acid and tributyltin, affecting genes such as BRAC1 [14,202–204].

Fewer reports describe histone modifications by environmental toxicants. The pesticide dieldrin is described to provoke a time-dependent increase in the acetylation of core histones H3 and H4 [205]. More recently, Li and co-workers [206] showed that bisphenol A or phthalate at exposure-relevant concentrations modulate macrophage inflammatory activities in association to H3 modifications. Increased H3 acetylation and methylation are also associated to human exposure to diesel-derived PM and metal-rich air particles [12]. Several histone deacetylase enzymes (HDAC1, 4, 6 and 7) and histone H3 proteins were modulated after Cr(VI) exposure and associated with the induced transcriptomic response [93]. Cr(VI) alters histone methylation [93], and cellular transformation was associated to increased levels of histone methyltransferases [207]. Notably, inhibition of methyltransferases decreased H3 methylation marks, DNA damage and malignant phenotypic properties in cells transformed by Cr(VI) [207].

In addition to the aforementioned epigenetic changes, environmental toxicants, such as diesel exhaust particles, can change the microRNA expression profile in connection with inflammation and tumorigenesis [208]. In fact, smokers present changes in the levels of different microRNAs, such as microRNA-296-5p, -3940, and -520d-3p [209], and changes of microRNA-21 expression is documented for various environmental toxicants, including arsenic, air and metal-rich PM [12,210]. Cr(VI) was also reported to increase cellular microRNA-21 expression and decrease microRNA-3940-5p levels in the plasma of exposed workers [93]. Downregulation of microRNA-3940-5p was shown in cells to enhance Rad51-mediated DNA repair [211], although prolonged exposure to Cr(VI) was argued in other study to inhibit homologous recombination repair [96]. In a cohort study that measured environmental pollutants and microRNA expression in placental samples, PBDEs were associated with increased microRNA-188-5p and decreased let-7c, whereas microRNA-1537 was upregulated by both PCBs and Cd, and several let-7 family members were inversely associated with Hg and Pb levels [212]. Several authors proposed microRNAs as biomarkers for acute and chronic environmental exposures due to their expression sensibility [213,214]. MicroRNA biomarkers can be a valuable approach for personalized medicine, to identify high-risk subjects and define interventions [46].

Polyphenols are able to regulate epigenetic states by different modes, including by modulation of DNA methyltransferase, histone acetyltransferase and deacetylase enzymes [215]. EGCG modulates the histone acetylation and deacetylation status by inhibiting histone acetyltransferases, and down-regulated NF-κB function and lymphocyte transformation [216]. In leukemia cells, EGCG down-regulated DNA methyltransferase 1, HDAC1 and 2, behaving as antiproliferative agent and anticancer epigenetic modifier [217]. Green tea polyphenols also reduced HDAC1, 2 and 3 expression, increasing H3 and H4 acetylation in human prostate cancer cells as well as the expression of GST-pi in correlation with DNA methyltransferase inhibition [218]. In addition to HDAC activity inhibition [218], green tea polyphenols induced proteasomal degradation of class I HDACs leading to cell cycle arrest and apoptosis in cancer cells [219]. Quercetin caused inhibition of p300 histone acetyltransferase activity [220] and, in human leukemia cells, it upregulated the Fas ligand-mediated apoptosis by inducing histone H3 acetylation and reducing HDAC activity [221]. Additionally, quercetin may promote H3 acetylation status by inhibiting SIRT6 [222].

Curcumin's antiproliferative activity was associated with inhibition of HDAC activity [223], reduction of HDAC1 and 8 protein expression with dose-dependent increases in H4 acetylation in parallel [224] and down-regulation of DAC4 expression [225]. Apigenin inhibited the activities of HDAC1 and HDAC3 enzymes in prostate cancer cells *in vitro* and *in vivo*, and resulted in histone H3 and H4 acetylation, increased p21 expression and apoptosis induction [226]. Genistein, another polyphenol, affected histone acetylation. This isoflavone was reported to modulate histone acetyltransferase activity and induce estrogen receptor-mediated histone acetylation [227]. It promoted acetylation of histone tails by upregulating histone acetyltransferase expression, enhancing expression of tumor suppressor genes in human prostate cancer cells [228]. Moreover, genistein also inhibited class III histone deacetylase SIRT1 [229]. The restoration of expression of BRCA1, p53 and p21 in human breast cancer cells by resveratrol was associated with the reduction of the enrichment of repressive histone methylation marks and increased abundance of activating histone acetylation marks within the proximal promoter region of those genes [230].

Regulation of microRNAs has been the epigenetic mechanism more studied up to now with polyphenols (Fig. 4), and harbors a great potential for chemoprevention since each microRNA can affect the translation of many target mRNAs [231]. Therefore, changes in the expression of microRNAs can alter the levels of many target proteins with wide implications for cell physiology. Furthermore, microRNAs transported in exosomes are found in extracellular media and blood, participating in tumor microenvironment (Fig. 5) and long-distance intercellular signals [231,232]. There is already a significant amount of published data on the microRNA expression changes induced by tea catechins, curcumin, quercetin and resveratrol [233–236]. The aggregated data on these top chemopreventive compounds obtained from different cellular and animal models enables the identification of a more precise group of microRNAs consistently regulated by the polyphenols: microRNA-1, -197, -21 and -296-5p (Fig. 4).

The four microRNAs regulated in common by tea catechins, curcumin, quercetin and resveratrol (Fig. 4) have all been connected to anticancer processes. MicroRNA-21 is a well-known oncogenic microRNA, associated to resistance and unfavorable progression of some cancers, and implicated in quercetin's inhibition of chromium (VI) malignancy [237,238]. However, it is remarkable that environmental toxicants provoke changes in microRNA-21 expression in different tissues [210]. MicroRNA-1 is deregulated in ovarian cancer and microRNA-197 was described as a predictor of poor prognosis in non-small cell lung cancer. MicroRNA-296-5p was associated with the prostate carcinogenesis [235,239,240] and was also shown to be affected in smokers [209].

To further deepen the cellular processes probably affected by polyphenol's regulation of those microRNAs, their protein targets were collected in mirTarBase website [241] and entered on STRING database [242] for representation as a functional network in annotated pathways (Fig. 4). The metabolic pathways more denoted in the obtained network were the signaling pathways regulating pluripotency of stem cells, the Jak-STAT, the Kaposi's sarcoma-associated herpesvirus infection, the viral carcinogenesis and the cytokine-cytokine receptor interaction signaling pathways. This analysis pointed to critical targets long related to carcinogenesis, as KRAS, PTEN or PIK3CA whose genetic mutations are associated to cancer, but also to proteins as STAT3 or cytokines, traditionally more associated to inflammation and immunity.

4.5. *Inflammation and immunomodulation*

Inflammation is an underlying denominator of many chronic diseases and environmental stressors-influenced pathologies [243]. Chronic inflammation combines with ROS and oncogenetic factors promoting carcinogenesis, by both genotoxic and non-genotoxic

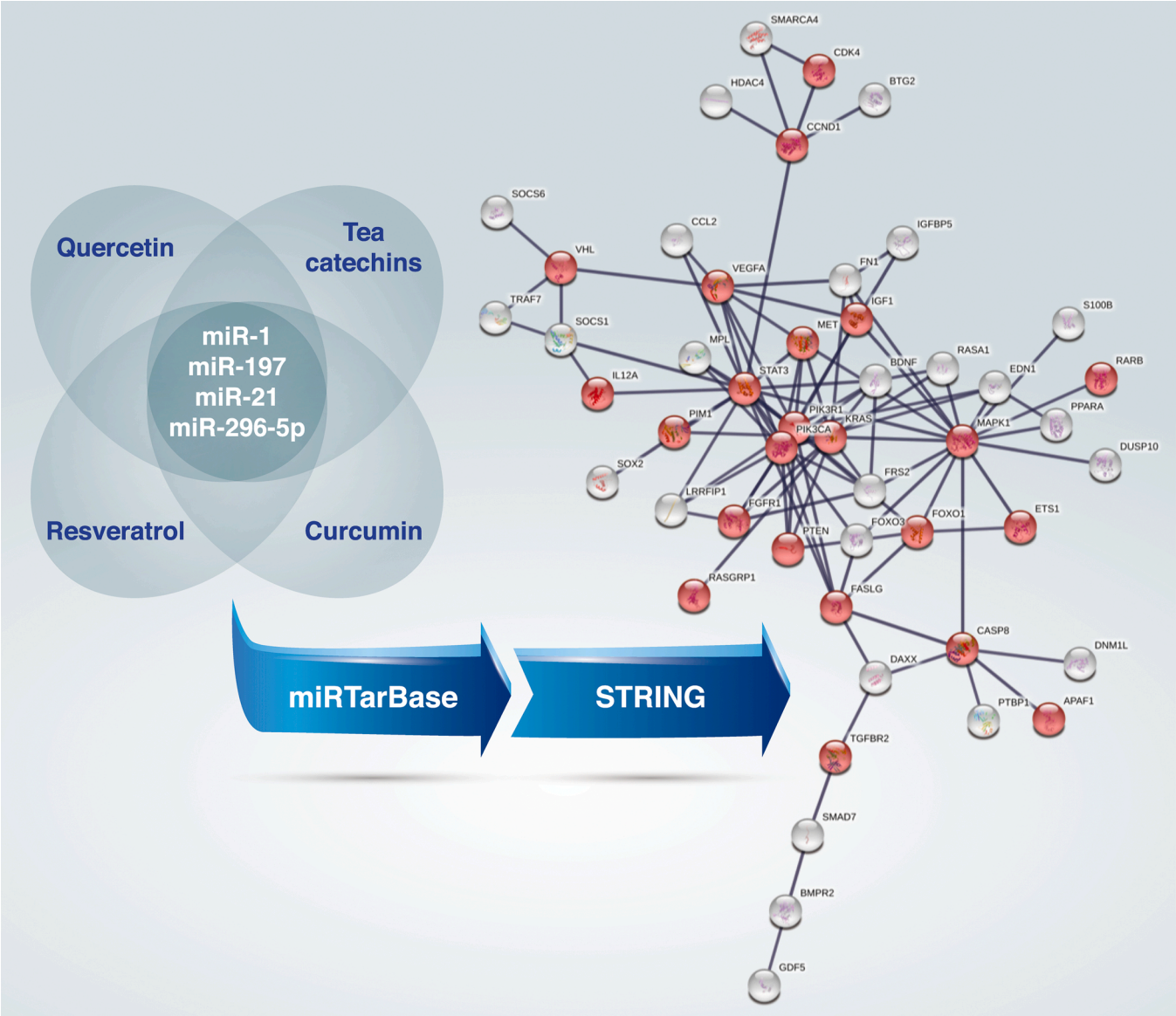

Fig. 4. MicroRNAs regulated by polyphenols in cancer and inflammation-related conditions and corresponding protein targets. Alterations in the expression of microRNAs induced by treatments with tea catechins, quercetin, curcumin and resveratrol were collected from varied studies in the references [233–236]. The protein targets of the 4 shared microRNAs regulated by the polyphenols were consulted at mirTarBase database (considered only the targets validated by all the following techniques providing strong evidence: reporter assay, PCR and Western Blot) [241]. The protein target list was introduced into the STRING database [242] and the represented network is for the highest score of confidence for minimum required interaction. Proteins marked in red make part of "Pathways in cancer" according to Kyoto Encyclopedia of Genes and Genomes.

mechanisms, so polyphenols' antioxidant and anti-inflammatory potencies are highly valued for prevention of cancer initiation and progression [44,123,244–247].

Activation of AhR induced the expression of the inflammatory IL-8 in cells exposed to dioxin [248], and increased the expression and activity of MMP-1, MMP-2 and MMP-9 together with an amplified invasion in keratinocytes and melanoma cell [249,250] (Fig. 1).

The transcription factor NF-κB is a major player in tumor-promoting inflammation (Fig. 5). Activation of NF-κB contributes to carcinogenesis by upregulating a broad range of genes enclosing pro-inflammatory cytokines, chemokines, MMPs, pro-proliferative and anti-apoptotic proteins, angiogenic factors, adhesion molecules and inhibitors of NFκB signaling [136,247]. As a consequence, all the cells present in the tumor microenvironment can be modulated by NF-κB signaling and sway inflammation, cancer initiation and progression. Furthermore, NFκB-induced chemokines recruit immune cells to cancer microenvironment [247] facilitating exosomes microRNAs' transport [251]. Indeed, miR-146, miR-155, miR-181b, miR-21 and miR-301a modulate NF-κB and vice versa [247]. Additionally, the Warburg effect also contributes to inflammatory processes [196] and can be stimulated by NF-κB which, in a positive feedback loop, is activated by glycolysis [247]. NF-κB activation can follow different pathways and be cell-type specific, with close relation to cellular ROS [136]. Thus, the ability of polyphenols such as apigenin, curcumin, EGCG, resveratrol and genistein to inhibit NF-κB signaling adds to their anticancer capacities to decrease ROS production and activate Nrf2 antioxidant response in transformed cells or at risk [125,127,139,197,252,253].

Jang et al. [25] presented very early the anti-inflammatory and antipromotion activity of resveratrol which was effective in reducing carcinogen-induced preneoplastic mammary lesions and skin cancer in mice. More recently, Jain et al. [141] used a prophylactic rat model of breast cancer initiated by DMBA, and found that resveratrol delayed

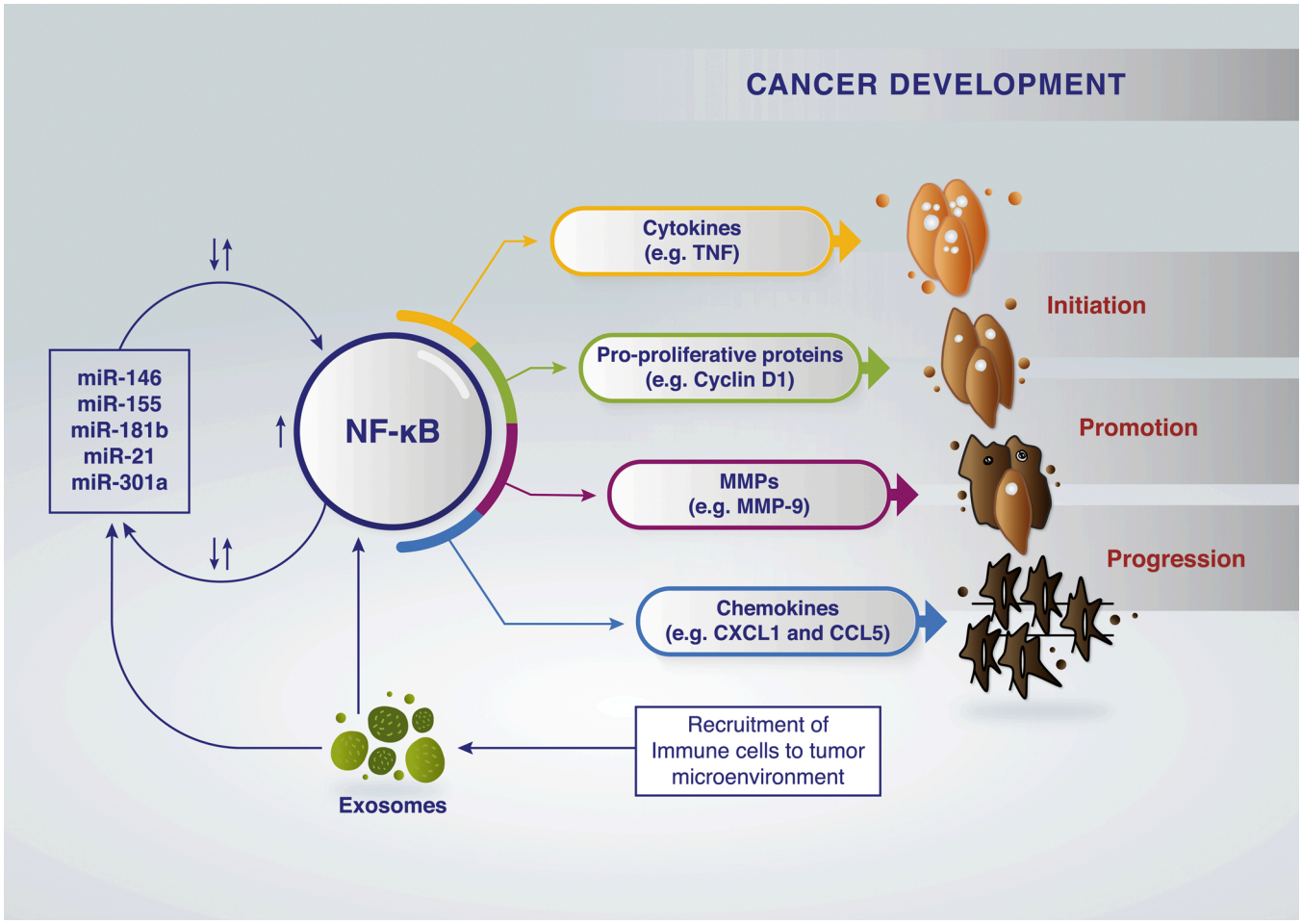

Fig. 5. Nuclear factor-κB (NF-κB) in cancer development. Activation of NF-κB influences the expression of microRNAs and vice-versa, and induces the expression of genes involved in cancer initiation promotion and progression as tumor necrosis factor (TNF), cyclin D1, matrix metalloproteinases (MMPs) and chemokine ligands. Additionally, NF-κB activation leads to the recruitment of immune cells to the tumor microenvironment. Abbreviations: CXCL1, C-X-C motif chemokine ligand 1; CCL5, C-C motif chemokine ligand 5.

tumor generation, progression and animal mortality, in association to decreased levels of inflammatory and angiogenic markers. In other chemical-induced carcinogenesis model, urethane-induced lung cancer in rat, preventive treatment with naringenin in nanoparticles reduced tumor volume, mortality and oxidative stress markers in the animal's lungs [254]. Very recently, silymarin also attenuated tumor burden of diethylnitrosamine-induced liver cancer in rats [254].

Pulmonary effects of airborne PM are also very connected to inflammatory process by way of activation of NF-κB and increased expression of IL-1β, IL-6, IL-8, MMP-9 and COX-2 [51,55]. Importantly, this pro-inflammatory response is dependent on redox signaling and MAPKs (ERK, JNK, p38), since it was attenuated by various antioxidants (vitamin C, quercetin, N-acetylcysteine) and MAPK inhibitors [51,55]. AhR signaling was also implicated in B[a]P-induced NADPH oxidase activation and priming of human macrophages superoxide anion production [79], although the role of AhR in PM-triggered inflammation is still unresolved [44]. Discussing the multiple mechanisms triggered by PM, Øvrevik et al. [44] denoted the extensive crosstalk between AhR and NF-κB signaling, and the importance of AhR in regulation of immune responses, in spite that dose thresholds for the activation of different mechanisms are unknown. Nevertheless, for opposing PCB pro-inflammatory effects, inhibition of AhR seems less effective than antagonizing NF-κB [255].

Oral administration of different polyphenols decreased B[a]P-induced changes in animal lung and other tissues, and resveratrol, quercetin, catechin, cyanidin and cyanidin-3-glucoside, all decreased tumor necrosis factor-α (TNF-α) expression *in vitro*, and resveratrol strongly inhibited neoplastic transformation at low micromolar concentration [110]. Consistently, quercetin inhibited production of pro-inflammatory cytokines TNF-α, IL-1β and IL-6 by pulmonary cells exposed to B[a]P or B[a]PDE, by a mechanism involving inhibition of the NF-κB and ERK pathways [256,257]. Moreover, quercetin prevented IL-6-driven activation of STAT3 and IL-6 enhancement of human bronchial epithelial cell transformation by B[a]PDE [256].

This anti-inflammatory action of polyphenols probably plays a role on the prevention of tumorigenesis induced by B[a]PDE *in vivo*, a carcinogen that does not requires metabolic activation [88]. Organ-on-a-chip models enabling the detailed analysis of inflammation, namely of lung and gut [258,259], could render useful information on the exact role of polyphenols in tumor microenvironment and inflammation-associated carcinogenesis.

Ulcerative colitis is an inflammation-associated premalignant condition that might progress to cancer, and in rodent models, colon-targeted delivery systems loaded with resveratrol and kaempferol inhibited inflammation and the enzyme sphingosine kinase 1 involved in the malignant progression [260,261]. Other common signaling routes are the Janus kinase/signal transducers and activators of transcription (JAK/STATs), which activate PIM (proviral integration site for moloney murine leukemia virus) kinase that, along with cyclin-dependent kinases (CDKs), phosphorylate pro-tumorigenic signaling proteins, such as Myc, Notch1 and BAD, but flavonoids may inhibit those kinases [262]. In a colonic cellular model, a flavonoid-rich extract combined the

antioxidant action, the inhibition of AhR, CYP1A1 and CYP1B1 expression, as well as IL-6 and IL-8, and the up-regulation of miR-146a that opposes NF-κB activation [263].

In an interesting human trial, black raspberries were applied as a gel in the tongue of patients with oral intraepithelial neoplasia, and a decrease in two inflammation-induced pro-inflammatory enzymes, cyclooxygenase 2 (COX-2) and inducible nitric oxide synthase (iNOS), was detected in the lesion's epithelium [264]. Moreover, the anthocyanin-containing gel suppressed genes involved in RNA processing, growth factor recycling and inhibition of apoptosis. Regulation of ROS, cell cycle, DNA repair and apoptosis mechanisms is also associated to prevention of inflammation and cancer in skin by flavonoids [265].

Concerning metal toxicants, polyphenols from different sources attenuated cadmium nephrotoxicity and systemic markers of inflammation in rats [266], increased the release of interferon-μ and IL-4, maintained the equilibrium between IL-10 and IL-17, and reduced NO release by peripheral blood mononuclear cells isolated from Ni-sensitized patients [267].

Inflammatory responses to PCBs have been investigated by different authors. In addition to NF-κB, molecular mechanisms associated to AhR and caveolae functions were implicated by different authors [78,83,135]. Recently, Wang et al. [255] found that PCB-126, but not PCB-153 or 118, induced the expression of inflammatory cytokines, including TNF-α and IL-1β in human monocytes/macrophages. Notably, PCB exposure in mice with compromised liver worsen overall inflammation as suggested by increased levels of circulating inflammatory biomarkers [195]. To ameliorate PCB and dioxin inflammatory mechanisms, hydroxycinnamic acids [268], quercetin [78,134], EGCG [80,83,135] and resveratrol [59,269] have shown positive effects.

Resveratrol given to pregnant and nonpregnant mice attenuated dioxin immunotoxicity, changes in the expression of T-cell receptor and costimulatory molecules, and T-cell differentiation, and reduced the expression of CYP1A1 in thymus of both the mother and the fetus [59]. Polyphenols show relevant immunomodulatory potential [197,270–272], still poorly explored in chemoprevention. Immune-mediated mechanisms of action of environmental toxicants are increasingly recognized, for instance in allergies, sensitivity reactions or autoimmunity [59,273,274]. However, it remains a challenge to address the complexity of immune deregulation implicated in those toxicant-induced conditions and in cancer triggering [2,274–276]. Besides NF-κB participation in immune responses [136,247], Thompson et al. [275] and Zhao et al. [274] reported other cancer-relevant molecular mechanisms targeted by bisphenol A, atrazine, phthalates and air pollutants: COX/prostaglandin E2, nitric oxide synthesis, epigenetic modifications, and regulation of T-cells, cytokines and chemokines [274,275]. Workers occupationally exposed to benzene presented oxidative stress markers, as well as decreased immunoglobulin levels, CD4 T-cells and CD4/CD8 ratio [277].

In experimental immunotherapy, curcumin induced changes in immune cells subsets in spleen and tumor tissues favoring immunosurveillance of malignant cells [271]. It is worth noting that curcumin increased T-cells and natural killer cells, among other effects in immune cells, when trialed for cancer therapy [278,279]. Flavonoids also display important immune capacities, including stimulation of CD4 T-cells and natural killer cells, which deserve further assessment in cancer prevention [270,280].

4.6. Gut microbiota and whole-body effects

Environmental toxicants and carcinogens can alter or disrupt intestinal microbiota (or flora), and thereby affect diverse physiological functions such as digestion, nutrient absorption, toxicant elimination and immunity [2,281–285]. Certain bacterial strains may also produce carcinogens [286]. On the other hand, gut microorganisms can transform environmental chemicals as metals, pesticides, polychlorobiphenyls and PAHs, influencing their toxic actions, both at the gastrointestinal tract and systemic toxicity [287–291]. For a very recent review of gut microbial metabolism of xenobiotics and connection to host hepatic function the reader is referred to the article by Clarke et al. [287].

When challenged by heavy metal or POP's exposition, common changes in gut microbiota include the decrease in phyla *Firmicutes*, increase in *Bacteroidetes* and increase in *Desulfovibrionaceae* [292,293]. PCB-126 at sub-micromolar concentration modulated the fermentative ability of a mouse fecal bacterial isolate, with cell membrane disruption implicated as mechanism of action [294].

Probiotic bacteria as *Lactobacilli* in animal models have shown capacity to modulate the toxicity of dangerous chemicals, such as heavy metals and pesticides, by ways of inhibiting absorption of toxicants, preserving intestinal barrier function or improving immune function [2,292]. Feng et al. [292] pointed the potential of probiotics for contaminants remediation *in vivo*. Concerning carcinogenic chemicals, microorganisms from species *Lactobacillus acidophilus*, *L. rhamnosus*, *Bifidobacterium longum*, *Saccharomyces boulardii*, *L. plantarum*, and *L. casei* showed protective roles against Cd, As, Cr(VI) and pesticide toxicities, namely, regulation of gut microbiota, lower genotoxicity, higher toxicant excretion in feces and reduced levels in body/tissues, decrease in oxidative stress, inflammation and in histopathological changes at different tissues and organs [292,295,296]. Gut microorganisms can therefore modulate local and whole-body threats of pollutants known to contribute for cancer development.

The capacity of polyphenols to modulate gut microorganisms is a growing research line. Bilberry polyphenols, green tea, EGCG, quercetin, resveratrol and piceatannol were reported to benefit gut microbiota balance in varied animal models, by increasing the bacterial diversity, regulating the *Firmicutes/Bacteroidetes* ratio, attenuating dysbiosis, favoring *Lactobacillus* and *Bifidobacterium*, while decreasing *Enterococcus faecalis* [297–301]. Polyphenols may protect bacteria in conditions of oxidative stress, as recently described for resveratrol and *L. reuteri* [302]. In healthy humans, 2-week treatment with green tea favored bacteria producers of short-chain fatty acids and the *Firmicutes/Bacteroidetes* ratio, among other changes associated to prevention of colorectal cancer [303]. Microbiota regulation by quercetin in mice was accompanied by promotion of short-chain fatty acids production and intestinal barrier integrity, and also by effects in inflammatory signaling, metabolism and cytochrome P450 2E1 expression at the liver [301].

Curcumin also showed several beneficial actions to the intestinal barrier function in conditions of chronic inflammation, including attenuation of IL-1beta secretion and induced disruption of the organization of tight junction proteins and paracellular transport [304]. Epithelial tight junction dysfunction and loss of intestinal barrier integrity, leading to paracellular transport of extracellular components, is closely associated to inflammatory disorders and may be an important target of polyphenols at the intestine with far-reaching implications for the body physiology [301,305]. In a rat model of obesity, resveratrol had less impact in the gut microbiota than quercetin, but greatly increased the expression of tight junction proteins as occludin [298]. A red wine polyphenol extract decreased the paracellular permeability of monolayers of colon epithelial cells [306]. In addition to restoring the expression of barrier-forming tight junction proteins, Nunes et al. [306] showed that the wine extract prevented the inflammation-induced increase in the channel-forming claudin-2. Reversing toxicant-induced changes in tight junctions can ensure the intestinal permeability barrier function and reduce toxicant leakage into systemic circulation [296].

5. Bioengineered models of carcinogenesis in early stages to study chemoprevention

The chemopreventive capacity of polyphenols has been studied for some time with several chemical-induced cancer models mentioned in previous sections, including DMBA, B[a]P and also B[a]PDE

carcinogens. Further preclinical models are being used to address more challenging conditions as carcinogenesis susceptibility of offspring from mothers exposed during gestation, epigenetic and transgenerational effects, and compelling results being obtained with resveratrol [59,307]. Genetically engineered animal models are also available, namely of prostate cancer [191], and incorporating features as the loss of PTEN [308] pertinent for investigating polyphenol molecular mechanisms (Fig. 4).

Clinical trials of chemopreventive polyphenols on different conditions are presented in the next section, but inflammation-associated premalignant conditions that can progress to cancer, such as Barrett's esophagus or ulcerative colitis, can be noted of interest to evaluate the potential of compounds and novel preparations. Curcumin is also being tested on asymptomatic plasma cell disorders which can give rise to multiple myeloma [309,310].

However, the study of cellular and molecular mechanisms of chemopreventive compounds requires further non-animal and human-relevant preclinical models valid to deepen the ability to block initiation and suppress cancer development [308,311]. Fenton and Hord described the transition of normal into initiated/preneoplastic cells with buildup of genetic alterations, dysplastic changes, altered cytokine and growth factor signaling, and apoptosis-resistant pro-survival phenotype [311]. Discussed in previous sections, emerging pro-carcinogenic contexts need to be accounted in cancer initiation, namely the participation of cellular bioenergetic changes and the role of tissue inflammation (Fig. 5).

Table 2 presents innovative *in vitro* systems providing useful tools for screening new compounds and gain a better understanding of their mode of action at early stages of cancer development. Gutleb previously reviewed models to study PM-induced toxicity, mostly cell culture models [54]. Emergent molecular, imaging and computational approaches are encouraged for novel technologies in cancer and toxicology research [2]. Replacing preclinical animal testing is being pursued, and for instance bioprinting adds advantages of automation, high-throughput screening, spatial control and fabrication of hierarchical structures. Definitely, the list of experimental tools in Table 2 reflects the investment on co-culture and three-dimensional (3D) models for their ability to better replicate the complexity of tissue conditions and provide greater *in vitro-in vivo* correlation compared to the classical two-dimensional (2D) models [312].

Table 2
Bioengineered and microphysiological models potentially useful for studying chemoprevention at early-stage carcinogenic or procarcinogenic conditions.

System	Features	References
Lung-on-a-chip	Alveolar-capillary interface with an elastic polymer membrane as barrier (microfluidic channels); cyclic stretching replicates physiological breathing.	[350]
Airway-on-a-chip	Microfluidic device with mucociliary bronchiolar epithelium and functional vascular endothelium, separated by porous polyester membrane, to mimic air flow and analyze lung pathophysiology (inflammation and infection).	[258]
Skin-on-a-chip	Device stacking multiple cell types, including epidermal, dermal fibroblasts and endothelial cells; investigation of skin inflammation and edema.	[351]
Gut-on-a-chip	Model allows the analysis of intestine–microbiome interactions, intestinal barrier function, bacterial growth, antibiotic therapies, intestinal inflammatory responses and the role of immune cells and microbes.	[259]
3D spheroid models	Mimics cellular heterogeneity, 3D microstructure, cell-cell physical contact and signaling observed in living tissues/tumor microenvironment.	[352]
Skin tissue equivalents	Models as EpiDerm, EpiSkin, Creative BioArray and SkinEthic permit genotoxicity, inflammation, UV exposure, DNA damage and omics studies.	[353]
3D Bioprinted skin models	Three-dimensional (3D) printed constructs producing full-thickness skin with melanocytes and keratinocytes, showing pigmentation, vascularization, and functionalities putatively enabling melanoma and pathology modeling.	[354,355]
3D Bioprinted models for drug testing	Flexible fabrication of 3D tissue models for pharmaceutical studies (efficacy and toxicology assays); scaffold-supported or -free models including different normal or cancer cells enable testing *in vitro* predictive toxicology, high-throughput screening, drug delivery and tissue-specific efficacies.	[312]
Cancer-on-a-chip	Platforms aimed to decompose or integrate the complex interactions within the tumor microenvironment, including tumor and immune cells, other stromal cells, soluble factors, and extracellular matrix; human-sourced tissues may be used for personalized medicine approaches.	[356,357]

6. Lessons from clinical trials

Clinical trials assessing chemopreventive potential of polyphenols in precancerous or cancer risk conditions were search at ClinicalTrials.gov (Table 3), and the trials found to have published results are organized in Figs. 6, 7, 8 and 9. Different terms were used for precancerous conditions: some examples entered at the search field "Condition or disease" were "Precancerous Conditions OR Precancerous Lesions OR Precancerous Skin Lesions OR Precancerous Changes of the Cervix OR premalignant OR chemoprevention OR cancer prevention". This search was combined with polyphenols search using the terms indicated in Table 3 and entered at the "Other terms" search field at the website. For trials without results at the ClinicalTrials.gov website, published studies of the Investigator were additionally searched on PubMed platform. It is to be noted that chemoprevention-related trials were found for tea catechins and other flavonoids, resveratrol and curcumin preparations (Figs. 6, 7, 8 and 9), but none with results concerning gallic acid, hydroxycinnamic acids (chlorogenic, ferulic and rosmaniric acids), theaflavin, procyanidins or capsaicin effects (Table 3).

The pharmacokinetic studies of green tea extracts, polyphenon E (a standardized green tea formulation) and EGCG, reveal accumulation of EGCG in bladder (NCT00666562) and esophagus (NCT00233935), but not in the prostate (NCT00459407) where no effects were observed on the number of cancer cases (NCT00596011) nor on biomarkers of cell proliferation, apoptosis and angiogenesis (NCT00253643, NCT00459407) (Fig. 6). Also, no effectiveness was observed for the recurrence rate of ovarian carcinoma (NCT00721890), nor human papillomavirus clearance or neoplasia (NCT00303823). No effect of EGCG ointment was also observed on actinic keratoses (NCT00005097). Though, in other cancer risk groups, the effectiveness of green tea extract, polyphenon E and EGCG was shown by decreasing the percentage of mammographic density in younger postmenopausal women similar to the age-dependent effect of tamoxifen (NCT00917735), by reducing marker of fumosin B1 intoxication associated to liver cancer [313] and by decreasing the number of relapsed cases of colorectal adenomas (NCT02321969). A 3-year trial of green tea extract on the recurrence of colorectal adenomas is now ongoing (NCT01360320). Additionally, in former smokers and in high-risk liver cancer subjects, the urinary excretion levels of DNA damage and lipid oxidation markers (8-OHdG and 8-iso-PGF2α) changed in the treatment group (NCT00363805, NCT02719860, [314]). In fact another study revealed that for heavy smokers within GSTM1 genotype, daily consumption of 4 cups of green tea leads to a significant decrease of the urinary 8-OHdG levels [315]. In a rare study with occupationally exposed subjects, pump workers exposed to benzene [316], green tea (900 ml i.e. 6 cups/day, 6 months) decreased urinary concentrations of benzene and

Table 3
Keywords used and number of studies returned in the search for polyphenol trials in cancer risk-related conditions for this work[a].

Keywords for polyphenol compound or group or herbal formulation	Results
Epicatechin OR Green Tea OR Polyphenon E	15
Resveratrol OR Grapes OR Stilbene	10
Curcumin OR C.I. 75300 OR C.I. Natural Yellow 3 OR Diferuloylmethane OR Turmeric Yellow	8
Anthocyanidin OR Anthocyanin OR Berries OR Black Raspberry	5
Silymarin OR Silibinin OR Silybin	4
Genistein	2
Quercetin	2
Gingerol OR Ginger	1
Hydroxytyrosol	1
Procyanidins OR Proanthocyanidins	1
Secoisolariciresinol	1
Capsaicin OR Pepper OR Eugenol OR Vanillyl OR Thymol OR Carvacrol	0
Celastrol OR Tripterine	0
Chlorogenic acid OR Chlorogenate OR Caffeoylquinate OR Caffeoylquinic acid OR Heriguard	0
Emtansine	0
Ferulic acid OR Rosmarinic acid OR Hydroxycinnaminic acids	0
Formononetin OR Biochanin B Or Formononetol	0
Gallic acid	0
Gambogic Acid	0
Hesperidin	0
Honokiol OR Magnolol OR Biphenol	0
Kaempferol	0
Lycobetaine	0
Melissa officinalis	0
Naringenin OR Naringetol OR Salipurol OR Salipurpol OR Trihydrixyflavonone	0
Sesamol OR Sesame oil	0
Theaflavin	0
Xanthohumol OR Chalcone	0

[a] The keywords were entered specifically at the search field "Other terms" and combined with precancerous condition OR cancer prevention search items at the website: https://clinicaltrials.gov.

phase I metabolites, while it increased GSH and reduced malondialdehyde levels in blood. These compelling results with tea polyphenols ask for further research on additional cancer hallmarks, namely to evaluate the modulation of enabling inflammatory signals.

Intervention studies with resveratrol in cancer risk groups also showed some positive results (Fig. 7). In healthy subjects over 50 years, the daily consumption of red fresh grapes (0.15–0.45 kg) for 2 weeks induced a decrease in the cancer-associated Wnt signaling pathway and related genes, especially in subjects with high dietary arginine consumption. In these cases, there was a higher expression of Wnt target genes, such as cyclin D1, AXIN2, cMYC and CD133 that decreased after the grapes ingestion period to levels observed in younger participants (NCT00578396). Additionally to these results, the authors also reveal that during the ingestion period participants lost on average 1.2 kg and that there was a decrease of mucosal proliferation. Freeze-dried grape powder inhibited the Wnt pathway in the normal colonic mucosa, but did not affect the same in the colon cancer tissue of patients (NCT00256334).

In a different study, the levels of activated caspase-3, an apoptosis marker, increased by 39 % in the resveratrol treatment group of subjects with colorectal cancer and hepatic metastases (NCT00920803). Nevertheless, resveratrol formulations provoke renal and gastrointestinal toxicity in multiple myeloma patients and in healthy subjects, respectively (NCT00920556, NCT00098969). As for pharmacokinetics, resveratrol presents rapid urinary excretion [317], but their metabolites were detected in mammary tissue, liver and colon, as well as in plasma (NCT03482401, NCT00920803, [318], NCT00098969 [317]).

An additional interesting chemopreventive trial of polyphenols is the study showing the effectiveness of a black raspberry gel in precancerous oral epithelial lesions in humans (NCT01192204). The treatment group showed a reduced size of lesions, histologic grades and loss of heterozygosity events (Fig. 8). A currently recruiting trial intends to study the pharmacokinetics of black raspberry metabolites and assess changes in DNA methylation (NCT03140280).

Moreover, previous studies detected other polyphenols in human body after treatment. Anthocyanins, genistein and silibin (active component of milk thistle and silymarin) were detected in blood, plasma and urine ([319], NCT00546039, NCT00487721), while curcuminoids were found in plasma and rectal tissue after supplementation (NCT01330810). Prolonged administration of secoisolariciresinol [320] and short treatment with higher doses of anthocyanins [319] afforded moderate reductions in proliferation indices (Fig. 8). However, in the case of curcuminoids (Fig. 9), no effects were observed in lower intestinal adenomatous polyps (NCT00641147), nor in several inflammation and proliferation markers, as well as, in aberrant crypt foci number (NCT00365209). However, in a small trial, combination of curcumin to quercetin reduced rectal polyps in patients with familial adenomatous polyposis [321]. Furthermore, intravaginal application of curcumin displayed no toxicity (NCT01035580), and a current study is analyzing the safety of curcumin in former smokers and its effect in occurrence of lung nodules (NCT03598309). Curcumin in a nanoemulsion formulation (NCT01975363) as well as hydroxytyrosol (NCT02068092), are being assessed in women at high risk of developing breast cancer. Other trial on curcuminoids (NCT02782949) plans to measure levels of inflammatory factors and DNA damage meaningful for evaluating the potential to prevent gastric cancer (Fig. 9). Encouraging results were reported for a curcumin-glycan delivery formulation that improved quality of life scores and redox status in occupational-related stress, with efficacy superior to standard curcumin [322], and decreased transaminases and inflammatory markers in chronic alcoholics [323].

Improvement in liver function and inflammatory biomarkers was also reported in one patient with advanced hepatocellular carcinoma after administration of silibinin (also called as silybin) [324], but short time treatments are not yielding favorable changes in proliferation markers [325]. Further findings on the effects of silibinin (and indole-3-carbinol) for 8 weeks on circulating inflammatory and immune markers as well as PIK3CA gene in smokers are waited from the trial NCT03687073. Phosphatidylcholine complexes afforded higher bioavailability of silibinin (NCT03440164) and led to detectable levels of silibinin in breast cancer tissue [325].

Noteworthy in colorectal cancer patients, and using significant doses or 12 months treatment, green tea consumption decreased the incidence of metachronous adenomas and relapsed cases of colorectal adenomas (NCT02321969), anthocyanins decreased proliferation [319] and resveratrol increased apoptosis markers in colorectal cancer with hepatic metastases (NCT00920803). Ginger root extract was also tested in subjects at risk of developing colorectal cancer (NCT01344538), and a dose of 2.0 g per day showed no apparent adverse effects and decreased arachidonic acid levels in normal colonic mucosa [326]. Concerning skin, spectroscopic approaches indicated oral administration of green tea increased the radical scavenging capacity of human skin, without significant changes in carotenoid levels [327].

Although human trials in conditions of exposition to environmental carcinogens are still scarce and mostly with smokers, the data collected in Figs. 6, 7, 8 and 9 regarding precancerous risk endorse specific polyphenols for cancer prevention applications (NCT00917735, [313], NCT00363805, NCT02719860, [314], NCT00578396, NCT01192204). Additional efforts are necessary to optimize treatment doses, schedule and delivery strategies. For example in trial NCT00459407 (Fig. 6), favorable results in a few biomarkers suggested a chemopreventive action, but not reaching statistical meaning perhaps because intervention was too short, single dose/day and participants were at an advanced illness condition [328]. Trial NCT00917735 also with tea polyphenols, but repeated dosing (twice daily) and prolonged time (12 months), yielded significant results for the subset of 50–55 years women [329]. Clearly the simplistic view of polyphenol antioxidants as panacea should be avoided, and the design of future trials may enable precise

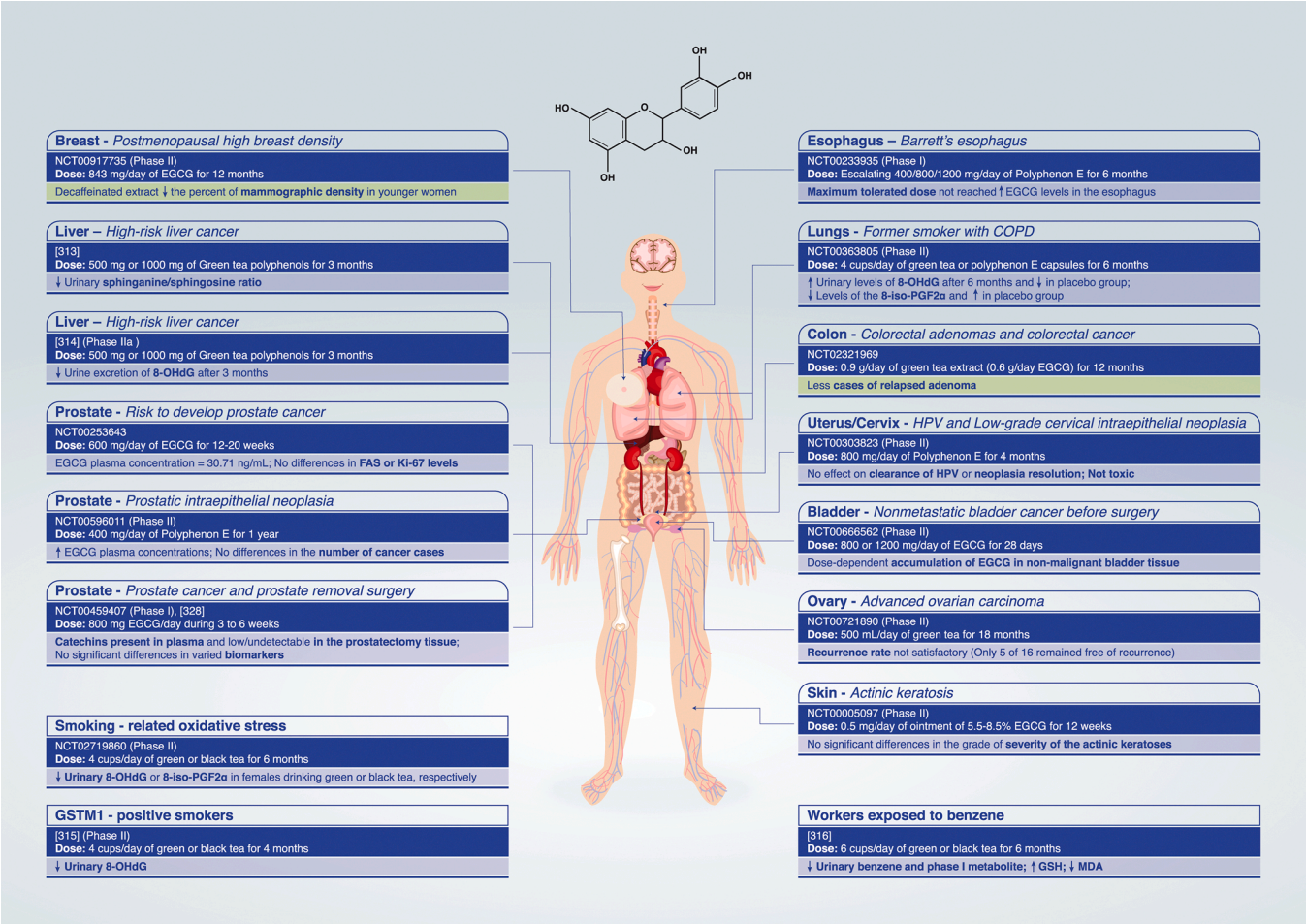

Fig. 6. Clinical trials of tea catechins in different cancer risk-related conditions. Information for each trial is divided in 3 levels corresponding to 3 horizontal rows: clinical condition of participants or trial purpose; trial reference, phase if applicable, polyphenol and dose; trial results including the reported outcomes in bold (stronger chemopreventive evidence in green). Trials are denoted by the ClinicalTrials.gov identifier or by a bibliographic reference. Molecular structure of epicatechin is represented. Abbreviations: ↓decrease; ↑increase; 8-iso-PGF2α, 8-iso-prostaglandin F2α (lipid oxidation marker); 8-OHdG, 8-oxo-2'-deoxyguanosine (DNA damage/repair marker); COPD, chronic obstructive pulmonary disease; EGCG, epigallocatechin-gallate; FAS, fatty acid synthase; GSH, reduced glutathione; GST, glutathione S-transferase; HPV, human papillomavirus; Ki-67, proliferation marker; MDA, malondialdehyde.

identification of subjects benefiting from novel formulations.

7. Implications for the design of protective interventions

The growing awareness of environmental toxicant exposure and bioaccumulation as a risk factor for noncommunicable diseases can be expected to promote development of nutritional protective interventions, functional foods and nutraceuticals.

Exposure to certain airborne pollutants, gaseous and PM in outdoor and indoor air, environmental carcinogens in foods, and also toxicant mixtures in occupational settings increase cancer risk (Table 1) and preventive measures are demanded for health protection [4]. It should be noted still that arsenic and cadmium have been found at alarming levels in drinking water through the world [330], adding to the inevitability of exposure to dangerous chemicals widespread in the environment.

Approaches combining exposure avoidance, education, clinical monitoring, adequate nutrition, excretion-stimulating exercise, among other general measures, are essential once pathological environmental contribution is suspected. However, certain individuals or groups at risk, heavy exposed or high burden (e.g. debilitated excretion), may be recommended specific prophylactic or therapeutic interventions.

The use of cancer preventive polyphenols is supported by abundant *in vitro* data, as well as by animal studies with different carcinogenesis models and epidemiological evidence referred in preceding sections. These results collectively highlight the potential of tea catechins, quercetin and resveratrol to counteract critical events in cancer initiation and development. Chemopreventive potential of green tea in breast cancer was recently strengthened by meta-analysis of several observational studies [331]. The human trials discussed in the previous section partially confirm the potential of these compounds, although success rates need improvement in coming interventions.

Drawbacks in clinical trials of antioxidants have been discussed by different authors. Noteworthy, antioxidant vitamins C and E can protect the lungs against short-term air pollution exposition [55,70]. In different settings, large-scale clinical trials of antioxidant vitamins A, C and E returned no significant effects and, in certain cases, unfavorable outcomes were observed [76]. However, limitations were pointed to large studies to assess the potential efficacy when patients are not routinely controlled for antioxidant deficiencies, actual blood levels and compliance [332–334]. Urinary polyphenol metabolites are alternative indicators of participant's compliance in clinical trials [329,335].

Moreover, the lack of methods to anticipate efficacious doses in humans pushes testing high antioxidant doses, disregarding prooxidant actions of vitamin C and other antioxidants. Translating doses tested in rodent models to human equivalent doses is probably incorrect because of species differences in xenobiotic metabolism and gut microbiota. In a different way, recent estimates from linear and non-linear

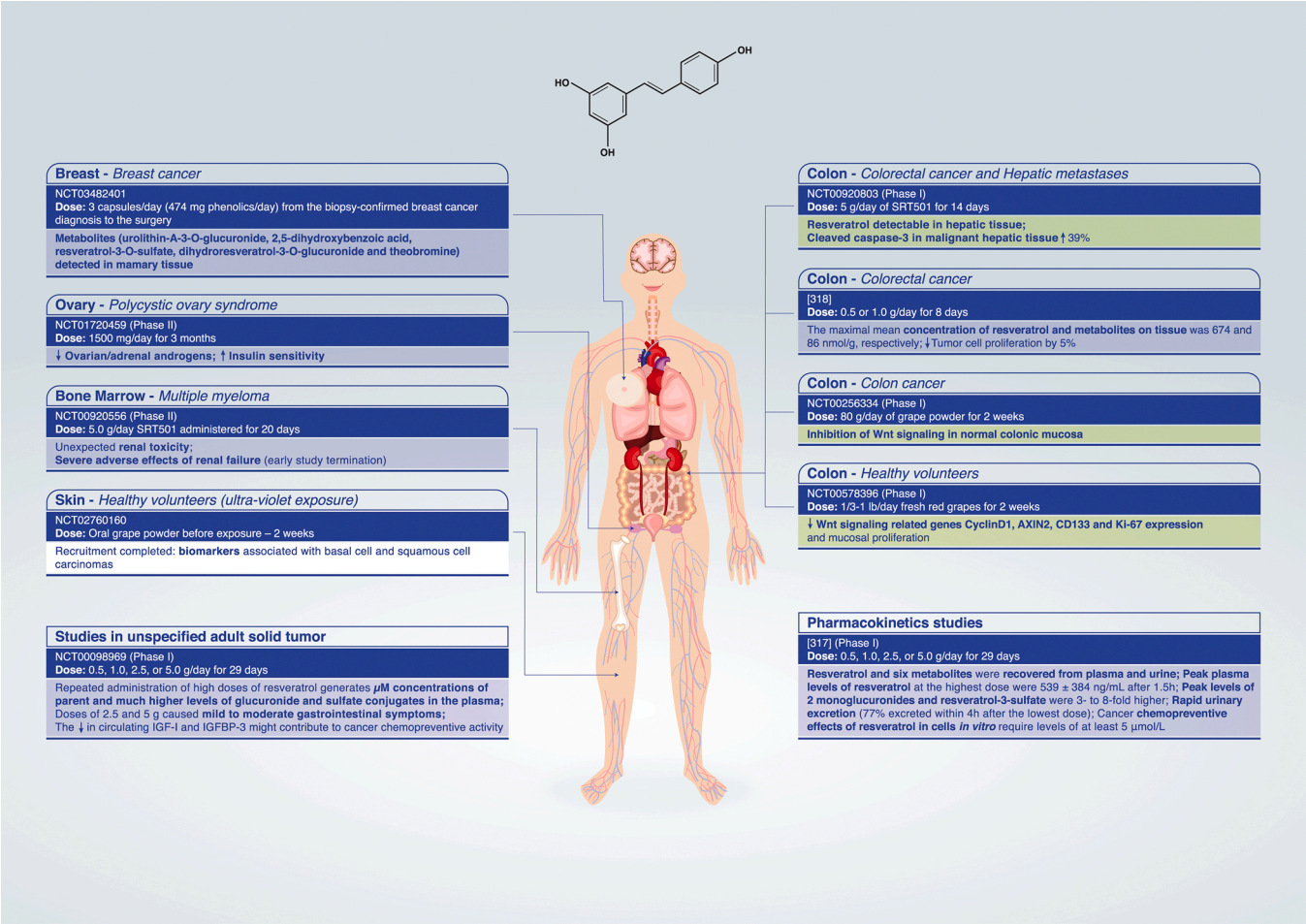

Fig. 7. Clinical trials of resveratrol and grapes in different cancer risk-related conditions. Information for each trial is divided in 3 levels corresponding to 3 horizontal rows: clinical condition of participants or trial purpose; trial reference, phase if applicable, polyphenol and dose; trial results including the reported outcomes in bold (stronger chemopreventive evidence in green; ongoing trials in white). Trials are denoted by the ClinicalTrials.gov identifier or by a bibliographic reference. Molecular structure of resveratrol is represented. Abbreviations: ↓ decrease; ↑ increase; AXIN2, cancer marker; CD133, cancer marker; Ki-67, proliferation marker; SRT501, resveratrol formulation.

dose–response meta-analyses of human studies, e.g. Parohan et al. [336] may assist optimization of doses of polyphenols and antioxidants to trial in the future.

Besides cost effectiveness, a steady advantage of plant-derived polyphenols is their safety profile. Albeit moderate concerns on the renal and hepatotoxicity and risk of intracerebral haemorrhage with catechins, and varied possible adverse actions of quercetin at high concentrations, traditional use and diverse human studies point to a good tolerability of flavonoids [272,316,337]. Regarding resveratrol (Fig. 7), adverse events were registered in human trials with some formulations only at high doses of 5 g/day (NCT00920556, NCT00098969). Abdominal discomfort, diarrhea and nausea were reported after curcumin doses of several grams/day [338].

The clinical trials discussed in the previous section indicate that prolonged oral supplementation provides significant concentrations of polyphenol forms in blood and accumulation in certain target tissues, although in several cases for preventive outcomes dosages were repeated over the day (NCT00363805, NCT02719860, NCT03476330, NCT01192204, NCT01402648, NCT00487721, NCT01330810), stressing the importance of optimized delivery schemes in interventions. Improved formulation for delivering higher dose or prolonged in time has been suggested to increase the therapeutic efficacy of black raspberries in humans [335]. It is essential to take in account that polyphenols can have important physicochemical and pharmacokinetic drawbacks, namely, low water solubility and bioavailability that limit their pharmacological efficacy. Diverse delivery systems are being developed to improve the stability and absorption as well as targeting of polyphenols [140,339,340]. Especially interesting for chemopreventive interventions, oral lipid-based carriers have been successfully enhancing the pharmacokinetics of various phytochemicals, and biocompatible polymer or lipid systems can ably deliver polyphenols to cells in skin, lung, colon and other critical tissues [140]. Adequate targeting of polyphenols may enable to reduce systemic concentrations and therefore avoid eventual adverse effects of high doses.

Varied proof-of-concept studies are becoming available for improvement of further applications. Green tea extract delivered by way of a subcutaneous implant reduced B[a]P-induced DNA adducts in rat lung [341]. In trial NCT01192204 (Fig. 8), topical applications of black raspberry gel through 6 weeks reduced lesion grade in most of the participants, while suppositories and other berry formulations alleviated oxidative stress and modulated detoxification (GST), inflammation and proliferation markers in esophagus or colorectal tissues in different human studies [319,335,342]. An oral lecithin-based phytosomal formulation that improves the pharmacokinetics of curcuminoids showed antioxidant, anti-inflammatory and immunomodulatory actions in leukemic and other cancer patients [278,279,343,344]. In leukemia patients, an immunoconjugate of genistein also afforded partial anticancer responses [345].

Facing the low success rates of previous trials of antioxidant vitamins, biomarker-guided approaches were proposed for selecting

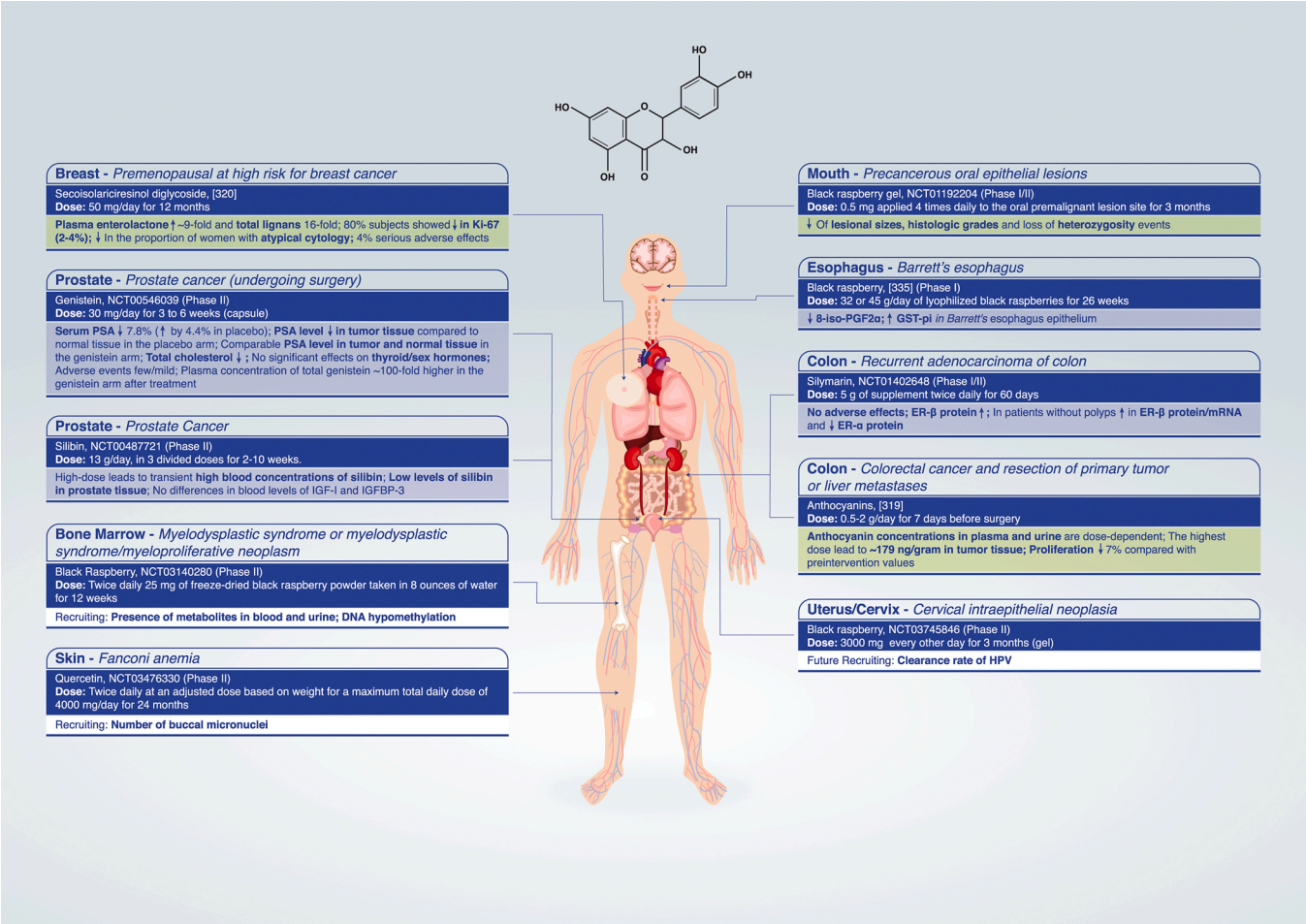

Fig. 8. Clinical trials of quercetin, black raspberries, silymarin, secoisolariciresinol and genistein in different cancer risk-related conditions. Information for each trial is divided in 3 levels corresponding to 3 horizontal rows: clinical condition of participants or trial purpose; trial reference, phase if applicable, polyphenol and dose; trial results including the reported outcomes in bold (stronger chemopreventive evidence in green; ongoing trials in white). Trials are denoted by the ClinicalTrials.gov identifier or by a bibliographic reference. Molecular structure of quercetin is represented. Abbreviations: ↓ decrease; ↑ increase; 8-iso-PGF2α, 8-iso-prostaglandin F2α (lipid oxidation marker); ER, estrogen receptor; GST, glutathione S-transferase; HPV, human papillomavirus; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; Ki-67, proliferation marker; PSA, prostate specific antigen.

participants and finding right doses to test [334]. Biochemical monitoring of participants is needed to follow compliance, pharmacokinetics, baseline and response markers [332,333]. Risk groups or subjects identified by using subclinical markers, e.g. lipid oxidation or DNA damage, will probably take more advantage from interventions [346, 347]. Illustrative studies of antioxidant supplementation found attenuation of oxidative stress only in subjects having low erythrocyte GSH levels [348] or in smokers with high body mass index [349].

Based on the preclinical and clinical data collected in this work, individuals at cancer risk due to environmental or occupational exposures may benefit from polyphenol interventions after proper evaluation, and proposals for trial's design are indicated:

- Groups under defined or steady expositions, as in occupational settings or air pollution, will probably offer more reproducible and translatable results;
- Individuals with previous symptoms, markers of subclinical injury or impaired function (e.g. low blood antioxidant or DNA damage repair capacity) should be prioritized for inclusion in trials monitoring the appearance of precancerous or toxicological outcomes;
- Green tea or catechin formulations (doses superior to 600 mg/day) and resveratrol (doses up to 2 g/day) are the oral supplementations more recommended by present data, namely for trials of breast and colon cancer prevention;
- Wine and green tea polyphenols, black raspberry and anthocyanins deserve continued study for protection against toxicant-induced gastrointestinal lesions;
- Curcumin and genistein may reveal useful for different cancer risks, namely leukemia, but additional validation is required;
- Doses administered shortly before and after predicted exposures may be beneficial, and treatments prolonged through several months have been affording positive results;
- Skin, respiratory tract and liver cancers are important risks associated to environmental exposures, and the preclinical data encourages clinical trials with catechins, resveratrol and curcumin;
- Formulations for improved pharmacokinetics and controlled release systems for dermal, buccal, pulmonary and colon-targeted purposes may be essential for successful applications.

8. Conclusions

A large body of evidence indicates that environmental toxicants are linked to cancer initiation, promotion and progression, and developing fetus, infant and children are more susceptible to toxic pollutant detrimental effects exerted through different genotoxic and non-genotoxic mechanisms of action. Dietary lifestyles are suggested to protect against toxicants by inducing their excretion from the body and activation of cellular innate defenses and repair systems. Although a direct

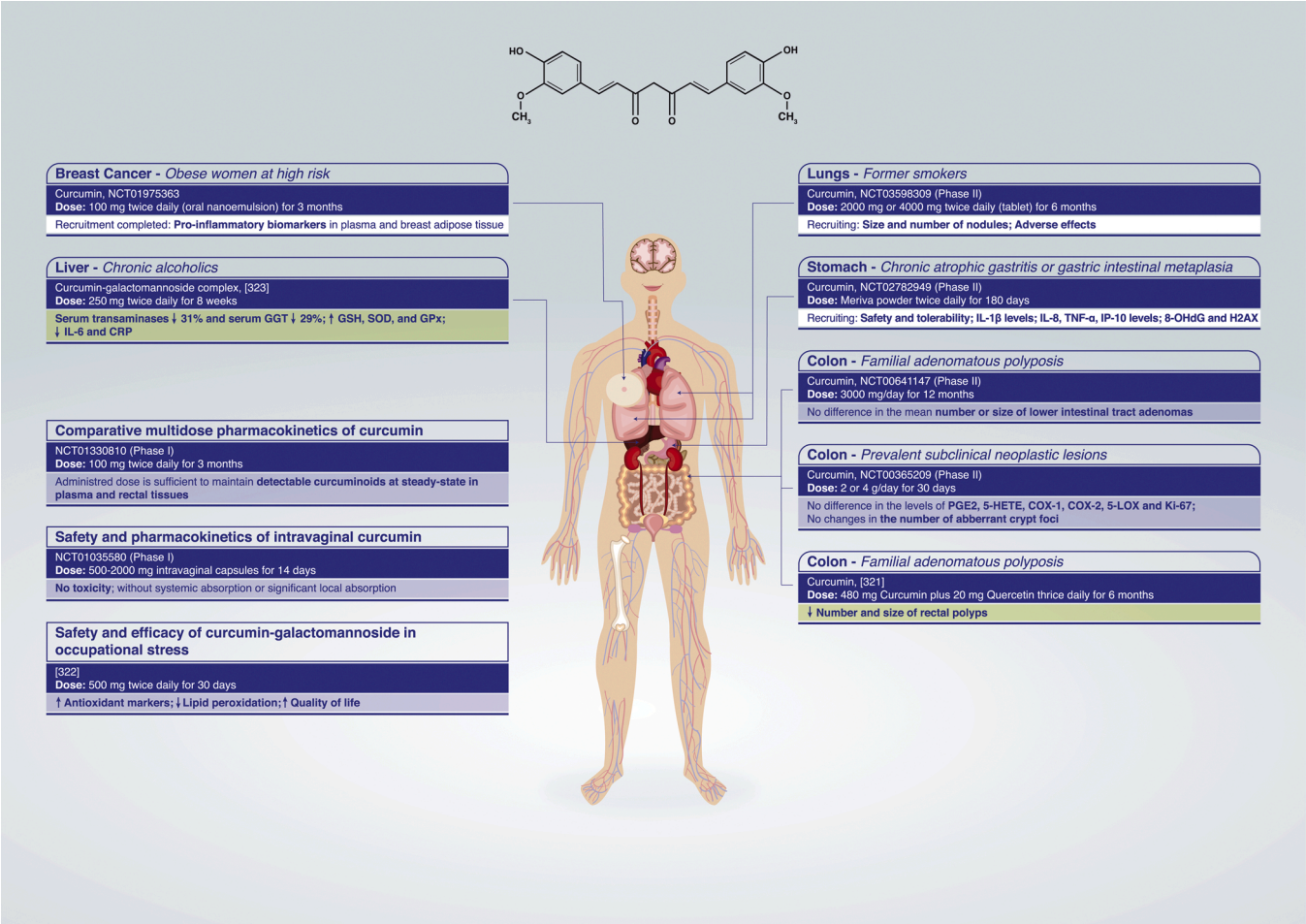

Fig. 9. Clinical trials of curcuminoids in different cancer risk-related conditions. Information for each trial is divided in 3 levels corresponding to 3 horizontal rows: clinical condition of participants or trial purpose; trial reference, phase if applicable, polyphenol and dose; trial results including the reported outcomes in bold (stronger chemopreventive evidence in green; ongoing trials in white). Trials are denoted by the ClinicalTrials.gov identifier or by a bibliographic reference. Molecular structure of curcumin is represented. Abbreviations: ↓ decrease; ↑ increase; 5-HETE, 5-hydroxy-eicosatetraenoic acid; 8-OHdG, 8-oxo-2'-deoxyguanosine (DNA damage/repair marker); COX, cyclooxygenase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; GPx, glutathione peroxidase; GSH, reduced glutathione; GST, glutathione S-transferase; H2AX, phosphorylated subtype of histone H2A; IL, interleukin; IP, inducible protein; Ki-67, proliferation marker; LOX, lipoxygenase; PGE2, prostaglandin E2; SOD, superoxide dismutase; TNF, tumor necrosis factor.

evidence of the protective activity of nutrients and nutraceuticals has not yet been elucidated, especially due to the different interactions between human variability and environmental factors, growing evidence suggests that polyphenols could prevent the onset of the conditions that promote cancer initiation. Over the last decades, the preventative, rather than curative, effects of polyphenols against cancer induced by environmental toxicants have been investigated, mainly by *in vitro* and *in vivo* studies on experimental animals. These investigations have hypothesized many different mechanisms of action ranging from antioxidant and anti-inflammatory activities, to the capacity to modulate calcium signaling regulation, which, in turn, increases the number of cell cycles inducing cell proliferation in different types of cancer, reduce toxicant-induced mitochondrial alterations and damage or alter the balance of gut microbiota in favor of a healthier composition. In addition, several studies have investigated the role of epigenetic changes linked to both negative and positive environmental factors, such as toxicants and nutraceuticals, respectively.

Polyphenols can block malignant transformation and control cancer progression through direct action on tumor-intrinsic factors and interplay with whole-body effects. Innovative models to study cancer development are expected to unravel critical mechanisms of action of toxicants and mixtures, potentially allowing to identify the best polyphenols for each risk condition. Nevertheless, the available data from *in vitro*, animal and human studies place tea catechins and resveratrol in the lead to counteract cancer initiation by environmental and occupational exposures. Other polyphenols such as curcumin, anthocyanins and silymarin, also present significant potential for protective treatments of individuals at high-risk.

Although promising results have been achieved by clinical trials performed on smokers or occupationally toxicant-exposed subjects consuming rich-polyphenol food or beverages, further clinical studies are needed to ascertain the possible preventative role of polyphenol treatments or food supplements containing bioactive polyphenols, especially considering their negligible adverse effects.

Finally, we recommend that future studies should be focused on:

- specific studies of the pharmacokinetic and pharmacodynamic properties in humans supporting the determination of daily doses of polyphenols that could exert a preventative effect considering both the dietary intake and supplementation;
- rigorous clinical trials on large cohorts of subjects, especially exposed to environmental toxicants to clearly define the protective effects of these natural compounds;
- increasing the efficacy of polyphenols by employing new delivery forms (i.e. solid lipid nanoparticle, microencapsulation, liposomal

delivery systems) and new dosage forms (for instance for sublingual absorption).

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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