1521-0103/350/3/483–494$25.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

http://dx.doi.org/10.1124/jpet.114.216333
J Pharmacol Exp Ther 350:483–494, September 2014

The Journal of PHARMACOLOGY And Experimental Therapeutics

Minireview

Translating Curcumin to the Clinic for Lung Cancer Prevention: Evaluation of the Preclinical Evidence for Its Utility in Primary, Secondary, and Tertiary Prevention Strategies

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Received May 7, 2014; accepted June 16, 2014

ABSTRACT

Lung cancer is responsible for over one million deaths worldwide each year. Smoking cessation for lung cancer prevention remains key, but it is increasingly acknowledged that prevention strategies also need to focus on high-risk groups, including ex-smokers, and patients who have undergone resection of a primary tumor. Models for chemoprevention of lung cancer often present conflicting results, making rational design of lung cancer chemoprevention trials challenging. There has been much focus on use of dietary bioactive compounds in lung cancer prevention strategies, primarily due to their favorable toxicity profile and long history of use within the human populace. One such compound is curcumin, derived from the spice turmeric. This review summarizes and stratifies preclinical evidence for chemopreventive efficacy of curcumin in models of lung cancer, and adjudges the weight of evidence for use of curcumin in lung cancer chemoprevention strategies.

Introduction

Lung cancer causes over one million deaths worldwide each year (Parkin et al., 2005; Lortet-Tieulent et al., 2014), and is the second most common cause of cancer in the UK (http://www.cancerhelp.org.uk/type/lung-cancer). Five-year survival remains at approximately 16%, with little improvement observed over the past 30 years (Gower et al., 2014), despite the advances made in surgical and therapeutic interventions. The most important risk factor for lung cancer is smoking, which accounts for up to 85% of all cases (Herbst et al., 2008). However, incidence of lung cancer in never smokers is also increasing, with estimates of disease within this cohort accounting for 15% of lung cancers in men and up to 50% in women (Parkin et al., 2005; Jemal et al., 2006; Couraud et al., 2012). Other environmental risk factors include secondhand cigarette smoke, cooking smoke, radon exposure, and exposure to environmental carcinogens, such as asbestos (Field and Withers, 2012; Hubaux et al., 2012). Susceptibility to lung cancer may also be increased by inflammatory conditions, including chronic obstructive pulmonary disease (COPD), pulmonary fibrosis (Sohal et al., 2013), scarring of lung tissues by infectious agents, such as tuberculosis (Liang et al., 2009), and by inherited cancer syndromes caused by germ line mutations in P53, retinoblastoma, and epidermal growth factor receptor (EGFR) (Oxnard et al., 2014).

Although lung cancers often present late, there are many possible avenues for intervention within both a surgical and chemopreventive context. Primary chemoprevention focuses on preventing the development of precancerous lesions particularly in high-risk populations, such as smokers; secondary prevention aims to prevent progression of preneoplasia to cancer; and tertiary prevention is concerned with prevention of spread or recurrence of primary disease (Keith, 2009).

Early disease can be classified into papillomas (squamous, glandular, or mixed) and adenomas (alveolar, papillary, salivary-gland-type). These preinvasive lesions can be further classified as squamous dysplasia/carcinoma in situ, atypical adenomatous hyperplasia, and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (Brambilla and Gazdar, 2009). There is currently ambiguity regarding the best way to treat early disease. Pulmonary nodules and atypical adenomatous hyperplasia are characterized by a radiologic ground-glass opacity, some of which may remain stable for years, and others which may be the precursors of adenocarcinomas (Nakahara et al.,

This work was supported by Cancer Research UK [C325/A6691] and the Leicester Experimental Cancer Medicine Centre [C325/A15575], funded by Cancer Research UK/UK Department of Health.
dx.doi.org/10.1124/jpet.114.216333.

ABBREVIATIONS: COPD, chronic obstructive pulmonary disease; EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; ROS, reactive oxygen species.

2001; Jeremy George et al., 2007; Bettio et al., 2012). With improved radiology in ground-glass opacity detection, and the question as to whether surgical intervention is appropriate in all cases, these lesions may present an ideal target for chemopreventive intervention.

Lung cancer itself can be divided into two main categories: small-cell lung cancer and non–small-cell lung cancer (NSCLC). Small-cell lung cancer is found primarily in smokers, with approximately 60% of patients presenting with widespread metastatic disease (most commonly to the brain, liver, or bone) at the time of diagnosis. NSCLC represents approximately 85% of all lung cancers, and can be subdivided into squamous cell carcinoma, adenocarcinoma, and large cell carcinoma, with adenocarcinoma being the most common disease in never smokers (Sun et al., 2007). Adenocarcinomas themselves may be further subdivided based on specific histologic subtyping (mixed subtype, acinar, papillary, solid, micropapillary, lepidic) (Travis et al., 2013). Adding to the complexity of this disease has been the observation that molecular subtyping can have a real impact on treatment outcomes. NSCLCs are now routinely tested for EGFR mutations and anaplastic lymphoma kinase fusions, which are altered in approximately 25% of adenocarcinomas (Shtivelman et al., 2014). This, in conjunction with histologic characteristics, guides targeted therapy treatment decisions. Further oncogenic drivers common to NSCLC include *BRAF, KRAS, PIK3CA, RET, HER2,* and *MET* (Munoz et al., 2013; Gower et al., 2014), which may exist within a tumor as multiple molecular drivers, ultimately leading to therapeutic resistance.

The primary intervention for lung cancer is smoking cessation, but a variety of interventional strategies may play important roles in other high-risk groups. Such strategies may include enhanced screening programs, dietary and lifestyle interventions, and chemoprevention.

Chemoprevention in Lung Cancer

Chemoprevention for solid tumors has had some success, particularly in colorectal cancer, yet there is currently little favorable clinical evidence to suggest success in lung cancer across a variety of both dietary and targeted agents (Szabo et al., 2013). A summary of chemoprevention trials for lung cancer is shown in Table 1. The majority of trials fit into the primary prevention category, targeting individuals at high risk. Many useful lessons have been learned from some of the largest trials to date for lung cancer prevention, most notably the Carotine and Retinol Efficacy Trial (Omenn, 2007). From this evidence, we now know that it is essential that chemoprevention trials take into account all preclinical data, including appropriate selection of models, understanding the mechanisms of action for the agents under investigation, understanding relevance of dose within a chemopreventive setting, targeting populations correctly, and giving due consideration to the likelihood of compliance in long-term intervention regimens (Szabo, 2006; Dragnev et al., 2013).

For a compound to be considered for use as a chemopreventive agent, it must have a very favorable toxicity profile, well studied pharmacokinetics (including comprehensive evaluation of stability and metabolism), known mechanism of action, proven efficacy in preclinical models, and be acceptable for long-term human consumption. It is for these reasons that many of the lung cancer chemoprevention trials to date have been undertaken using chemicals that occur naturally within the diet. One such chemical that meets many of the aforementioned criteria, which has yet to be assessed clinically for chemopreventive efficacy in lung cancer, is the dietary agent curcumin.

Curcumin

Curcumin is derived from the spice turmeric, and has been extensively investigated for its chemopreventive potential. The putative mechanisms of action for curcumin are numerous, among which are its radical scavenging activity and anti-inflammatory, antiproliferative, antiangiogenic, proapoptotic, and immune-modulatory properties (Irving et al., 2011). In addition, it has been used safely in a number of early-phase clinical trials for colorectal cancer, pancreatic cancer, Alzheimers' disease, breast cancer, multiple myeloma, ulcerative colitis, rheumatoid arthritis, and COPD (http://clinicaltrials.gov/ct2/results?term=curcumin&pg=3). Despite much promise as a putative chemopreventive agent, clinical utility of curcumin for indications outside of the gastrointestinal tract has been considerably hindered by its lack of bioavailability (Anand et al., 2007). There is accumulating research, however, into a variety of formulations and administration methods (reviewed in Flora et al., 2013; Subramani and Narala, 2013; Prasad et al., 2014) which may increase the potential of curcumin for use in a wider variety of disease states. These formulations include coadministration with piperine, curcumin nanoparticles, liposomal encapsulation, phospholipid complexing, structural analogs of curcumin, formulation with oligosaccharides, and more recently, the potential for curcumin to be administered via a pressurized metered dose inhaler (Subramani and Narala, 2013). The ability to deliver systemically concentrations of curcumin that have proven biologic activity in preclinical models opens up a real possibility for use of curcumin in lung cancer chemoprevention regimens.

This review will summarize and stratify preclinical evidence for chemopreventive efficacy of curcumin in models of lung cancer published over the past 10 years. Model and dose selection will be discussed in the context of primary and tertiary chemoprevention regimens, and the weight of evidence for use of curcumin as a lung cancer chemopreventive agent adjudged.

Models for Primary Lung Cancer Prevention

Despite the fact that many of the clinical studies investigating lung cancer prevention fit the primary prevention model, there are relatively few in vitro and in vivo studies which assess efficacy of curcumin in "high-risk" models (Tables 2 and 3). The favored in vitro model for assessment of primary intervention strategies using curcumin is the BEAS-2B bronchial epithelial cell line treated with environmental carcinogens including fine particulate matter (Zhang et al., 2012), cadmium (Rennolds et al., 2012), or cigarette smoke (Shishodia et al., 2003). Curcumin appeared able to protect against inflammation in response to these agents, most notably by inhibition of proinflammatory cytokines and prevention of translocation of nuclear factor-κB, a transcription factor which acts as a central mediator of the immune response, to the nucleus. Only one study has used primary human lung fibroblasts, in which curcumin downregulated markers of lung fibrosis (Tourkina et al., 2004). None of the concentrations of curcumin used in these studies (0.5–50 μM) would likely be

TABLE 1
A selection of clinical studies for chemoprevention of lung cancer (primary, secondary, and tertiary prevention strategies) stating outcome of study

Year	Phase	Agent	Dose Regimen	Study Group Biomarker/Endpoint	1°, 2°, or 3° Prevention	Patient No.	Conclusion	Reference
2013	III	Selenium	200 μg/d for 48 months	Pretreated for stage I lung cancer. Time to second primary tumor	Tertiary	156	No benefit	Karp et al., 2013
2006	III	1) Retinol and zinc 2) Riboflavin and niacin 3) Ascorbic acid and molybdenum 4) β-Carotene, α-tocopherol, and selenium	Doses ranged from 1 to 2 times the US Recommended Daily Allowances for a period of 5 years	Smokers	Primary	29584	Nonsignificant	Kamangar et al., 2006
2001	III	Isotretinoin	30 mg/d for 3 days	Treated for stage 1 NSCLC Second primary tumor Time to recurrence and death	Tertiary	1166	Negative/harmful	Lippman et al., 2001
2000	III	*N*-Acetylcysteine/ retinyl palmitate (vitamin A)	1) Retinyl palmitate (300,000 IU daily for 1 year followed by 150,000 IU for a second year) 2) *N*-Acetylcysteine (600 mg daily for 2 years) 3) Both compounds 4) No intervention	Treated for NSCLC second primary tumor	Tertiary	2592	Nonsignificant	van Zandwijk et al., 2000
1996	III	β-Carotene/ retinoic acid (vitamin A) in form of retinyl palmitate	30 mg of β-carotene per day and 25,000 IU of retinoic acid (vitamin A) for an average of 4 years	Smokers Asbestos exposure	Primary	18314	Harmful	Omenn et al., 1996
1996	III	β-Carotene	50 mg on alternate days for 12 years on average	Smokers: 11% Ex-smokers: 39% Nonsmokers: 50%	Primary	22071	Nonsignificant	Hennekens et al., 1996
1993	III	α-Tocopherol/ β-carotene	α-Tocopherol 50 mg/d β-Carotene 20 mg/d for 5–8 years	Smokers	Primary	29133	Harmful/negative	The ATBC Cancer Prevention Study Group, 1994
2013	II	Enzastaurin	500 mg/d or placebo for 6 months	Former smokers	Primary	40	Nonsignificant	Gray et al., 2013
2012	II	Sulindac	150 mg/day for 6 months	NSCLC/current or former smokers	Primary Secondary Tertiary	61	Nonsignificant	Limburg et al., 2013
2011	II	Iloprost	50 mg/d placebo	Current/former smokers Sputum atypia Endobronchial dyplasia	Primary	152	Significant improvement of endobronchial histology in former smokers	Keith et al., 2011
2011	IIb	Celecoxib	800 mg/d or placebo for 6 months	Former smokers	Primary	137	Potential efficacy	Mao et al., 2011
2011	II	Budesonide	800 μg twice daily or placebo for 1 year	Current/former smokers	Primary/secondary Changes to peripheral nodule size	202	Nonsignificant Trend toward decreased size in nonsolid nodules	Veronesi et al., 2011
2010	II	Celecoxib	200/400 mg or placebo twice daily for 3–6 months	Current/former smokers	Primary/secondary Changes to proliferation index in bronchial epithelium	204	Significant decrease in Ki67 immunoreactivity at high dose	Kim et al., 2010
2009	II	13-*cis* RA ± α-tocopherol	13-*cis* RA at 50 mg/d or 13-*cis* RA plus α-tocopherol at 800 mg/d, or no active treatment	Sputum atypia	Primary	75	Nonsignificant	Kelly et al., 2009
2005	II	Oltipraz	400 mg/wk, 200 mg/wk, or placebo	Chronic smokers	Primary	77	Nonsignificant	Kelley et al., 2005

(*continued*)

TABLE 1—*Continued*

Year	Phase	Agent	Dose Regimen	Study Group Biomarker/Endpoint	1°, 2°, or 3° Prevention	Patient No.	Conclusion	Reference
2004	IIb	Budesonide	800 mg twice daily or placebo for 6 months	Smokers Dysplasia of bronchial epithelium	Secondary	112	Nonsignificant	Lam et al., 2004
2002	IIb	Anethole Dithiolethione	25 mg three times daily for 6 months	Smokers with bronchial dysplasia	Primary	112	Potentially effective–significantly lower progression in treated group	Lam et al., 2002
2000	II	Retinamide	200 mg daily for 6 months	Squamous metaplasia and dysplasia	Primary	82	Nonsignificant	Kurie et al., 2000
1995	II	β-Carotene/ retinoic acid	500 mg β-carotene/d and 25,000 IU of retinol/day on alternate days for 5–8 years	Sputum atypia	Primary	755	Nonsignificant	McLarty et al., 1995
1994	II	Isotretinoin	1 mg/kg for 6 months	Metaplasia	Primary	86	Nonsignificant	Lee et al., 1994
1994	II	Folate + vitamin B12	10–20 mg/d folate and 750 μg/d vitamin B12 for 1 year	Squamous metaplasia	Primary	57	Beneficial effect	Saito et al., 1994
1992	II	Etretinate	25 mg daily for 6 months	Sputum atypia	Primary	150	Negative	Arnold et al., 1992
1992	II	β-Carotene	20 mg/d for 14 weeks	Frequency of micronuclei in sputum	Primary	114	27% lower micronuclei count in treated group	van Poppel et al., 1992
1988	II	Folate + B12	10 mg of folate plus 500 μg of hydroxocobalamin for 4 months	Sputum atypia	Primary	73	Reversal of sputum atypia	Heimburger et al., 1988

RA, retinoic acid.

achievable in human lung tissue following oral dosing of standard nonformulated curcumin. T_{max} plasma levels following curcumin doses of 3.5–12 g daily have previously been observed to be in the order of 11 nM to 1.7 μM, with tissue levels in the colorectal mucosa equating to approximately 50 μM, but remaining at the limits of detection for tissues distant to the gastrointestinal tract (Garcea et al., 2004; Howells et al., 2007; Irving et al., 2013). In vivo models explored lung injury induced by a variety of mechanisms, which bear relevance to the type of insult that human lungs would be exposed to. Administration of tobacco-related carcinogens and lung injury–inducing insults [infectious agents and diesel exhaust particles administered intratracheally (Kalpana and Menon, 2004; Vanisree and Sudha, 2006; Xu et al., 2007, 2014; Suzuki et al., 2009; Bansal and Chhibber, 2010; Malhotra et al., 2011, 2012a; Sehgal et al.,

TABLE 2
In vitro data alluding to potential utility for curcumin in primary lung cancer chemoprevention strategies

Year	Model	Observations	Reference
2014	Beas-2B bronchial epithelial cells	Induction of ubiquitin-activating enzyme E1-like (UBE1L) leading to a decrease in EGFR at 0.5–10 μM curcumin.	Jiang et al., 2014
2013	Fetal rat lung fibroblasts	Prevention of hyperoxia–causative factor in bronchopulmonary dysplasia. Curcumin at 5 μM prevents hyperoxia-induced increases in apoptosis, and prevents ERK1/2 phosphorylation.	Sakurai et al., 2013
2012	Human bronchial epithelial cells	Curcumin pretreatment (30 minutes at 10–40 μM) prevents induction of inflammation (decreased NFκB, IL-6) in response to fine particulate matter.	Zhang et al., 2012
2011	Calu-3 human bronchial epithelial cells	Curcumin (10–50 μM) prevents cadmium-induced upregulation of proinflammatory cytokines IL-6 and IL-8, with consequent reduction in ERK1/2 phosphorylation.	Rennolds et al., 2012
2009	Goat lung homogenate	Curcumin (50 μM) prevents nitric oxide–induced inactivation of cystatin (a cysteine proteinase inhibitor that provides protection against pulmonary fibrosis).	Khan et al., 2009
2004	Primary lung fibroblasts derived from scleroderma patients	Curcumin (6–10 μM) causes apoptosis in scleroderma but not normal lung fibroblasts. Curcumin downregulates the abnormal PKCε observed in sclerodermal fibroblasts.	Tourkina et al., 2004
2003	Beas-2B bronchial epithelial cells	Curcumin (50 μM) prevents cigarette smoke carcinogen (CSC)–induced activation of NFκB, and CSC-dependant IκBα degradation.	Shishodia et al., 2003

ERK1/2, extracellular signal-related kinase 1/2; IκBα, inhibitory κBα; IL, interleukin; NFκB, nuclear factor κB; PKCε, protein kinase Cε.

TABLE 3
A selection of in vivo data alluding to potential utility for curcumin in primary lung cancer chemoprevention strategies

Year	Model	Observations	Refence
2014	C57BL/6 mice with intratracheal inoculation of *Staphylococcus aureus*	Curcumin (50 mg/kg i.p.) attenuated *S. aureus*–induced acute lung injury by decreasing inflammatory cell infiltration, decreasing alveolar wall thickening and consequent edema.	Xu et al., 2014
2013	Male Sprague-Dawley rats (18Gy single radiation dose to thorax)	Daily curcumin (200 mg/kg) preirradiation and for 8 weeks postirradiation inhibits radiation-induced macrophage accumulation, interstitial edema, alveolar septal thickening, and perivascular fibrosis.	Cho et al., 2013
2013	Newborn Sprague-Dawley rats under hyperoxia conditions	Curcumin (daily i.p. for 5 days, 5 mg/kg) decreased oxidant injury and maintained alveolar integrity.	Sakurai et al., 2013
2013	Female CBA/J mice with intranasal inoculation of reovirus	Curcumin (50 mg/kg 5 days prior to inoculation) attenuated viral-induced inflammation and fibrosis, in addition to reducing inflammatory cytokines IL-6, IL-19, and IFNγ.	Avasarala et al., 2013
2012	Wistar rats treated with cyclophosphamide	Curcumin (200 mg/kg daily gavage for 14 days) decreased cyclophosphamide (CP)-induced lung oxidative stress and IL-1β levels, in addition to attenuating CP-induced lung fibrosis and collagen proliferation.	Hamdy et al., 2012
2012	Male TO mice exposed to diesel exhaust particles (DEP)	Curcumin (45 mg/kg, 1 hour prior to each DEP exposure) significantly inhibited inflammatory cell infiltration into lungs. Curcumin also significantly inhibited DEP-induced systemic inflammation.	Nemmar et al., 2012
2012	Male Laka mice exposed to benzo[a]pyrene (BP)	Curcumin (60 mg/kg daily oral dose 10 days prior to BP administration and for 12 days postadministration) significantly improved mitochondrial structure and decreased lung edema.	Malhotra et al., 2011, 2012b
2012	Male Sprague-Dawley rats with sepsis-induced acute lung injury	Curcumin (50 or 200 mg/kg i.p. 2 hours postsepsis induction) significantly attenuated pulmonary edema and inflammation, increased superoxide dismutase activity, decreased malondialdehyde, TNFα, and IL-8. Survival was increased by 40%.	Xiao et al., 2012
2012	Mice with *Escherichia coli* LPS-induced lung injury	Pulmonary administration of water-soluble curcumin administered intratracheally (30 μg, 2 hours postinitiation) attenuates lung injury and edema.	Suresh et al., 2012
2012	Male Swiss mice treated with benzo[a]pyrene	Curcumin in combination with piperine shows pronounced antioxidant effects (100 and 20 mg/kg respectively, 2 hours pretreatment prior to BP administration) by preventing BP-induced superoxide dismutase, catalase and glutathione depletion.	Sehgal et al., 2011, 2012
2010	Balb/c mice infected with *Klebsiella pneumoniae*	Daily oral curcumin (150 mg/kg given for 15 days preinfection) significantly decreased pulmonary neutrophil infiltration, decreased malondialdehyde production, and downregulated TNFα.	Bansal and Chhibber, 2010
2009	C57BL/6J mice exposed to cigarette smoke (CS)	Curcumin (100 mg/kg by gavage administered 1 hour prior to each CS exposure) significantly decreased neutrophils and macrophages in bronchoalveolar lavage and significantly attenuated CS-induced air space enlargement.	Suzuki et al., 2009
2007	Female Sprague-Dawley rats—bleomycin-induced pulmonary fibrosis	Daily oral curcumin (250 or 500 mg/kg daily postinduction for 28 days) significantly downregulated Col-I, TGFβ1, and iNOS.	Xu et al., 2007
2006	Wistar rats exposed to cigarette smoke	Daily oral curcumin (80 mg/kg for 2 weeks coadministered with cigarette smoke) attenuated the CS-induced changes to pulmonary histology and decreased inflammation.	Vanisree and Sudha, 2006
2004	Wistar rats exposed to nicotine	Curcumin (80 mg/kg i.g. for 22 weeks) decreased nicotine-induced alkaline phosphatase, lactate dehydrogenase, and lipid peroxidation levels, in addition to enhancing antioxidant status.	Kalpana and Menon, 2004

Col-I, type I collagen; IFNγ, interferon γ; i.g., intragastric; IL-6, 19, 1β, interleukin 6, 10, 1β; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; TGFβ1, transforming growth factor β1; TNFα, tumor necrosis factor α.

2011, 2012; Hamdy et al., 2012; Nemmar et al., 2012; Suresh et al., 2012; Xiao et al., 2012; Avasarala et al., 2013; Cho et al., 2013)] resulted in pulmonary edema, alveolar wall thickening, inflammatory cell infiltration, and fibrosis. These symptoms were attenuated by curcumin (most often delivered orally) at doses typically in the region of 50 mg/kg, which would equate to a dosing regimen of approximately 3.5 g/d for a 70 kg human. However, there is little evidence within the primary chemoprevention setting to definitively equate promising changes at the molecular level with an ultimate decrease in tumor burden.

Models for Secondary Lung Cancer Prevention

Moghaddam et al. (2009) describe one of the few models which fit into the secondary prevention category. Oral curcumin

TABLE 4
A selection of in vitro data alluding to potential utility for curcumin in tertiary lung cancer chemoprevention strategies

Year	Model	Observations	Refence
2014	PC-9, H1975, H1650 NSCLC cell lines	Curcumin increased cytotoxicity of erlotinib in erlotinib-resistant cell lines. It enhanced erlotinib-induced apoptosis, downregulated EGFR, p-EGFR, surviving, and inhibited NFκB activation in erlotinib-resistant cell lines.	Li et al., 2014a
2014	Large-cell lung carcinoma cell line 801D	Curcumin (10–60 μM) inhibits viability, EGFR and TGFβ1-induced migration, Rac1 protein expression, MMP2, and MMP9.	Chen et al., 2014
2013	A549, H460, BEAS-2B cell lines	Synthetic monocarbonyl analog of curcumin (B85) inhibits proliferation and induces apoptosis via activation of endoplasmic reticulum stress-mediated pathway.	Liu et al., 2013
2013	H460, A549 cell lines	Solid lipid nanoparticle curcumin inhibits growth and induces apoptosis with an IC_{50} 4- to 5-fold lower than for native curcumin.	Wang et al., 2013b
2013	A549 cell line	Curcumin (5–40 μM) increases the Bax:Bcl-2 ratio, causing apoptosis via mitochondrial cytochrome c release.	Li et al., 2013
2013	A549, IMP-90 (lung fibroblast)	Curcumin (50 and 100 μM) induces LC3-II resulting in autophagy. Concomitant increases in phosphorylation of AMPK and ACC observed.	Xiao et al., 2013
2014	A549 cell line	Hydrazinobenzoylcurcumin (10–80 μM) induced autophagosome formation in a time- and dose-dependent manner, in conjunction with accumulation of LC3-II.	Zhou et al., 2014
2012	A549 cell line	Curcumin sensitizes cells to redox-mediated apoptosis. Apoptosis is accompanied by decreased ratio of glutathione:oxidized glutathione and increased p38 MAPK phosphorylation.	Kaushik et al., 2012
2013	A549, H1299, H460, PC9 cell lines	Curcumin (5–100 μM) augments erlotinib-induced apoptosis and increases IκB.	Yamauchi et al., 2014
2014	A549, H460 cell lines	Curcumin (1–50 μM) causes growth inhibition via cell cycle arrest, mediated by increased p21 and p27 and decreased cyclin D1. An increase in FOXO1 is caused by curcumin-induced increase in ERK1/2 phosphorylation.	Li et al., 2014b
2013	A549 cell line	Curcumin-loaded nanoparticles demonstrated enhanced cytotoxicity compared with native curcumin.	Yin et al., 2013a
2013	A549 cell line	Curcumin analog 4-arylidene curcumin inhibits NFκB by acting as an irreversible deubiquitinase inhibitor of the 19S regulatory particle, and reactivates p53.	Zhou et al., 2013b
2013	A549 cell line	Curcumin nanoparticles (5–100 μM) inhibited TNFα-induced ICAM-1 expression and TNFα-induced ROS expression.	Yen et al., 2013
2013	A549 and cisplatin-resistant A549 cell lines	(1*E*,4*Z*,6*E*)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(5-methylfuran-2-yl)hepta-1,4,6-trien-3-one (2a), a novel curcumin analog (1.56–100 μM), causes greater growth inhibition in cisplatin-resistant cells. This is accompanied by inhibition of thioredoxin reductase activity leading to intracellular ROS generation and induction of apoptosis.	Zhou et al., 2013a
2012	NCI-H446, NCI-H1688 small-cell lung cancer (SCLC) cell lines	Curcumin (15 μM) inhibits IL-6–induced proliferation, migration, and invasion of SCLC cells and causes G2N cell cycle arrest. Also inhibits IL-6–induced STAT3, JAK1,2, and 3 phosphorylation, and downregulates MMP2, MMP3, VEGF, survivin, Bcl-$_{XL}$, and ICAM-1.	Yang et al., 2012a
2012	A549 and cisplatin-resistant A549 cell lines	Curcumin (10–40 μM) inhibits growth in cisplatin sensitive and resistant cell lines to a similar extent, but sensitizes resistant cells to apoptosis via caspase-3 activation. Curcumin inhibits HIF-1α and decreases p-glycoprotein levels.	Ye et al., 2012
2012	A549, 95D, 901D, 95C, BEAS-2B cell lines	Curcumin (5–20 μM) inhibits migration and invasion of 801D cells, inhibits Cdc42 expression and Cdc42-regulated expression of invasion and metastasis genes (PAK1, cofilin).	Chen et al., 2012
2012	AALE normal bronchoepithelial cells, H441 cells	Curcumin (1–50 μM) inhibits proliferation and STAT3 phosphorylation in both cell lines.	Alexandrow et al., 2012
2012	NCI-H446 (SCLC) cell line	Curcumin causes apoptosis by mitochondrial-mediated pathways, inducing Bax expression and decreasing expression of Bcl-2 and Bcl-$_{xL}$, concurrent with an increase in intracellular ROS.	Yang et al., 2012b
2012	A549, H1299	Curcumin (2.5–40 μM) inhibits cell growth, which is synergistically enhanced when combined with small-molecule inhibitors against EGFR, IGF1R, FGFR, PI3K, and NFκB.	Lin et al., 2012
2011	H460	Curcumin analog (1*E*,4*E*)-1,5-bis(2,3-dimethoxyphenyl)penta-1,4-dien-3-one upregulates C/EBP homologous protein (CHOP) to stimulate the ER stress-mediated apoptotic pathway.	Wang et al., 2011
2011	A549, H460, SPC-A1	Bisdemethoxy (BDMC) and demethoxy curcumin (DMC) had greater hypomethylation effects than curcumin (20–100 μM). BDMC and DMC decreased hypomethylation in WIF-1 promoter resulting in restoration of WIF-1 protein levels.	Liu et al., 2011
2012	NCI-H441, CCL-151 (normal fibroblast) cell lines	Curcumin analog 4-[3,5-bis(2-chlorobenzylidene-4-oxo-piperidine-1-yl)-4-oxo-2-butenoic acid] (CLEFMA) caused rapid depletion of glutathione:oxidized glutathione ratio and induction of ROS in cancer cells only.	Sahoo et al., 2012
2010	A549 cell line	Curcumin downregulates miRNAs miR-186, 625, 576, 39, 9, let7e, and upregulates miRNAs miR-320, 26a, 16, 130a, 125b, 23a, 23b, let7i.	Zhang et al., 2010a

(*continued*)

TABLE 4—*Continued*

Year	Model	Observations	Refence
2010	A549, H1299 cell lines	Curcumin (10 μM, 2 h prior to nicotine induction) inhibits nicotine-induced phosphorylation of Akt, ERK1/2, JNK, and p38, and decreases protein levels of Cox2, cyclin D1, Bcl-2, and inhibitors of apoptosis.	Puliyappadamba et al., 2010
2010	PC-9, A549 cell lines	Curcumin (25–50 μM) upregulated growth arrest and DNA damage inducible genes (GADD) 45 and 153, concomitant with upregulation of p21 and p27 and downregulation of Bcl-2.	Saha et al., 2010
2010	H460 cell line	Curcumin (5–50 μM) promoted G2/M cell cycle arrest and induced caspase-3, -8, and -9 activity. Decreases in Bcl-2, Bcl-$_{xL}$, and XIAP were observed in conjunction with increases in Bad, Bax, and FAS.	Wu et al., 2010
2010	A549 and cisplatin-resistant A549 cell lines	Curcumin (10–50 μM) induces apoptosis in the drug-resistant cell line by downregulating miR-186.	Zhang et al., 2010b
2010	A549 cell line	Curcumin (5–40 μM) induces apoptosis by a mitochondrial-mediated mechanism leading to cleavage of caspases-3 and -9 and PARP. Ratio of Bax:Bcl-2 is significantly enhanced.	Chen et al., 2010b
2010	H460, BEAS-2B cell lines	Curcumin (0.25–5 μM) sensitizes lung cancer cells to anoikis-induced cell death via inhibition of Bcl-2 and ROS generation.	Pongrakhananon et al., 2010
2010	A549 cells	Curcumin (20–40 μM) significantly downregulates eIF2α, eIF4E, and phospho-4E-BP1, and upregulates phospho-eIF2α and phospho-eIF4E.	Chen et al., 2010a
2009	A549 cells	Curcumin (10–20 μM) inhibits migration and invasion, and downregulates PI3K, PKC, VEGF, cjun-p, Ras, GRB2, MEKK3, FAK, MKK7, JNK, ERK, MMP2, MMP9, and RhoA.	Lin et al., 2009
2010	A549 cells	Curcumin (10–50 μM) decreases the activity of the Pokemon promoter by preventing recruitment of its transcriptional activator, SP-1.	Cui et al., 2010
2009	H460 cells	Curcumin (50–100 μM) reverses cisplatin resistance and enhances cisplatin-induced apoptosis by induction of intracellular ROS and proteosomal degradation of Bcl-2.	Chanvorachote et al., 2009
2008	CL1-5 cells	Curcumin (1–20 μM) decreased invasion and migration associated with increased expression of the tumor suppressor HLJ-1. HJL-1 is transcriptionally upregulated following a curcumin-induced increase in binding of the transcription factor AP-1.	Chen et al., 2008
2008	A549 cells	Curcumin (5–50 μM) prevented the IFNα-induced increase in NFκB by downregulating protein expression of its p50 and p65 subunits, leading to a consequential decrease in COX2 activity.	Lee et al., 2005
2005	H520 cells	Curcumin (25 μM) enhanced the apoptotic response of vinorelbine.	Sen et al., 2005
2004	CL1-5 cells	Curcumin (1–20 μM) inhibited invasion at low doses. Microarray analysis and protein verification revealed inhibition of NCAM, MMP14, and TOPO-IIa, and upregulation of heat shock protein family members.	Chen et al., 2004

AALE cells, tracheobronchio epithelial cell line; ACC, acetyl-CoA carboxylase; AMPK, 5′AMP-activated protein kinase; AP-1, activator protein-1; Bad, BCL2-associated agonist of cell death; Bcl-2, B cell lymphoma-2; COX2, cyclooxygenase-2; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; eIF2α, eukaryotic translation initiation factor 2α; eIF4E, eukaryotic translation initiation factor 4E; ER, estrogen receptor; ERK1/2, extracellular signal-related kinase 1/2; FAK, focal adhesion kinase; FAS, tumor necrosis factor receptor superfamily, member 6; FGFR, fibroblast growth factor receptor; FOXO1, forkhead box O1; GRB2, growth factor receptor-bound protein 2; HIF-1α, hypoxia inducible factor-1; HLJ-1, DNA J-like heat shock protein-1; IκB, inhibitory κB; ICAM-1, intracellular adhesion molecule-1; IGF1R, insulin-like growth factor 1 receptor; IFNα, interferon α; IL, interleukin; JAK, Janus kinase; JNK, c-Jun N-terminal activated kinase; LC3-II, microtubule-associated protein light chain 3-II; MAPK, mitogen-activated protein kinase; MEKK3, mitogen-activated protein kinase kinase kinase 3; miRNA, micro RNA; MKK7, mitogen-activated protein kinase kinase 7; MMP2/9, matrix metallopreotease 2/9; NCAM, neural cell adhesion molecule; NFκB, nuclear factor κB; PAK1, P21 protein (Cdc42/Rac)-activated kinase 1; PARP, poly ADP ribose polymerase; p-EGFR, phosphorylated epithelial growth factor receptor; PI3K, phosphatidyl inositol 3 kinase; PKC, protein kinase C; Rac-1, Ras-related C3 botulinum toxin substrate 1; Ras, rat sarcoma; RhoA, Ras homolog gene family, member A; SP-1, specificity protein-1; STAT3, signal transducer and activator of transcription 3; TGFβ1, transforming growth factor β1; TNFα, tumor necrosis factor α; TOPO-IIa, topoisomerase IIa; VEGF, vascular endothelial growth factor; WIF-1, Wnt inhibitory factor-1; XIAP, X-linked inhibitor of apoptosis.

(1% in the diet) was found to inhibit lung tumor formation in a conditional K-ras–induced mouse model, mimicking COPD-like airway inflammation induced by nontypeable *Haemophilus influenzae* (Moghaddam et al., 2009). Serum curcumin levels at this dose equated to approximately 2 μM, but parent curcumin was undetectable in lung tissue. Tissue levels of 40 ng/mg protein were observed for both demethoxy and bisdemethoxy curcumin.

Models for Tertiary Lung Cancer Prevention

The in vitro data for tertiary prevention using curcumin are presented in Table 4. Although use of established cancer cell lines has therapeutic inference, it also follows that clinical maintenance strategies postresection/chemotherapy would fit within this paradigm for prevention of recurrence. However, when contextualizing the presented data, it is likely that many of the studies described here used established lung cancer cell lines due to ease of obtaining and maintenance of these cell lines, rather than direct targeting and tailoring of preclinical research toward translationally relevant endpoints. Several studies presented in Tables 4 and 5 directly reflect a chemotherapeutic approach, as they combine curcumin with therapeutic drugs. The possibility of applying such combinations clinically may again have potential for use in adjuvant or maintenance regimens, and so for the purpose of this review, are included within the tertiary prevention section.

Of the 38 studies presented, 24 (63%) use the NSCLC adenocarcinoma cell line A549, and 18 studies present data derived from a single cell line only. Most of the studies again used curcumin at concentrations in excess of those likely to be achieved in the lung following oral dosing with standard curcumin, which has not been formulated to specifically

TABLE 5
A selection of in vivo data alluding to potential utility for curcumin in tertiary lung cancer chemoprevention strategies

Year	Model	Observations	Reference
2013	Female C57 mice bearing LL/2 cell xenograft	A novel formulation of curcumin/doxorubicin-loaded methoxy poly (ethyleneglycol) (MEG)-PCL nanoparticles (i.v. every 5 days for 15 days) had greater antitumor and apoptosis-inducing efficacy than either agent alone.	Wang et al., 2013a
2013	Female nude mice bearing A549 xenograft	Solid lipid nanoparticle curcumin (SLN) and native curcumin (200 mg/kg i.p. daily for 19 days) exhibited 32-fold higher levels in lung than native curcumin, and decreased tumor growth by >3-fold compared with native curcumin.	Wang et al., 2013b
2013	Female nude mice bearing A549 xenograft	Curcumin (500 mg/kg per day) given in conjunction with phospho-sulindac synergistically inhibits tumor growth and improves bioavailability of phospho-sulindac in xenograft tissue.	Cheng et al., 2013
2013	Female Balb/c-nu mice bearing A549 xenograft	Curcumin analog 4-arylidene curcumin (1 and 5 mg/kg i.p. once every 5 days for 20 days) significantly decreased tumor growth, reactivated p53, and inhibited NFκB signaling.	Zhou et al., 2013b
2013	C57BL/6 mice with TNFα aspirated into lungs	Curumin nanoparticles (200 mg/kg i.p. prior to TNFα) decreased ICAM-1 expression in lung alveolar epithelial cells.	Yen et al., 2013
2013	Nude mice bearing A549 xenograft	Curcumin nanoparticles (15 mg/kg) decreased tumor growth to a greater extent than nonformulated curcumin.	Yin et al., 2013b
2012	Male C57BL.6 with tracheal instillation of LLC cells	Curcumin-cyclodextrin complex (3 mg/kg) potentiates the effects of gemcitabine to significantly decrease tumor volume and proliferative index (Ki67).	Rocks et al., 2012
2012	C57BL/6J mice bearing LL/2 xenografts	Liposomal curcumin (5 mg/kg per day for 14 days) enhanced antitumor activity of radiation dose delivered to the thorax. Curcumin decreased the onset of radiation pneumonitis and enhanced tumor response in combination with radiation.	Shi et al., 2012
2012	Nude mice bearing A549 xenograft	Curcumin (15 mg/kg i.v.) synergistically enhanced the antitumor efficacy of docetaxel.	Yin et al., 2012
2011	VEGF-overexpressing transgenic mice	Curcumin (5 mg/kg i.p. three times weekly for 5 months) decreased pulmonary function damage, decreased pulmonary inflammation, and decreased mRNA levels of *vegrf, kdr, nrp-1, c-myc, egfr, erk2,* and *cyclin a*.	Tung et al., 2011
2010	Female C57BL/6 mice with tracheal instillation of LLC cells	Curcumin (1% or 5% in diet) prevented pulmonary fibrosis following thoracic irradiation (13.5 Gy), but did not enhance antitumor efficacy of radiation.	Lee et al., 2010
2010	Balb/c$^{nu/nu}$ mice bearing NCI-H460 xenografts	Curcumin (30 or 45 mg/kg per day i.p.) inhibits tumor growth.	Su et al., 2010

ICAM-1, intracellular adhesion molecule-1; kdr, kinase insert domain receptor; NFκB, nuclear factor κB; nrp, neuropilin; PCL, poly-ε-caprolactone; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

enhance bioavailability. Overwhelmingly, mechanisms of action reported for the antitumor efficacy of curcumin in lung cancer cells are via mitochondrial-mediated cell death elicited by an increase in the Bax:B cell lymphoma-2 ratio or by an increase in intracellular reactive oxygen species (ROS) (Chanvorachote et al., 2009; Pongrakhananon et al., 2010; Saha et al., 2010; Wu et al., 2010; Wang et al., 2011, 2013b; Sahoo et al., 2012; Yang et al., 2012a,b; Li et al., 2013; Liu et al., 2013; Xiao et al., 2013; Chen et al., 2014). Migration and invasive capacity of lung cancer cells may be further decreased by inhibition of matrix metalloprotease expression, decreased nuclear factor-κB, EGFR, Akt, signal transducer and activator of transcription 3, and Cdc42 signaling (Chen et al., 2004, 2012, 2014; Lee et al., 2005; Lin et al., 2009, 2012; Puliyappadamba et al., 2010; Kaushik et al., 2012; Liu et al., 2013; Yamauchi et al., 2014; Zhou et al., 2013a; Li et al., 2014b). Although drug resistance in lung cancer is a primary cause for therapeutic failure, very few in vitro models of resistance have been used when investigating the potential of curcumin for tertiary interventional strategies. The A549/CDDP cell line was developed by intermittent administration of cisplatin to native A549 cells (Pan et al., 2009), and is one of the few artificially generated models of resistance that has been used for assessing utility of curcumin to overcome drug resistance. However, some cell lines (PC9, H1975, H1650) become resistant to targeted drugs such as the tyrosine kinase inhibitors (e.g., erlotinib, gefitinib) and have thus been used to expand the potential utility of curcumin to lung cancers harboring/gaining specific mutations. Cotreatment using standard chemotherapy drugs in combination with curcumin enhanced antitumor efficacy of erlotinib (Yamauchi et al., 2014; Li et al., 2014a), cisplatin (Chanvorachote et al., 2009; Ye et al., 2012; Zhou et al., 2013a), and vinorelbine (Chen et al., 2004) by sensitizing cells to drug-induced apoptosis.

In vivo data for tertiary prevention are shown in Table 5. Xenograft models bearing A549 or Lewis lung carcinoma cells provide the majority of data in which curcumin has observable antitumor efficacy, but there are few concurrent mechanistic data to evaluate. Orthotopic models created via intratracheal instillation of lung cancer cells (Lee et al., 2010; Rocks et al., 2012) provide better insight as to whether an antitumor effect of curcumin could be maintained at the correct pathologic site. In all but one of the studies cited, either formulated curcumin or curcumin analogs were used to enhance bioavailability. Curcumin/curcuminoids were also used in conjunction with chemotherapy agents doxorubicin (Wang et al., 2013a), phosphosulindac (Cheng et al., 2013), gemcitabine (Rocks et al., 2012), docetaxel (Yin et al., 2012), or radiation (Lee et al., 2010; Shi et al., 2012). No studies took advantage of testing these novel formulations of curcumin, or combinations of curcumin with cytotoxic agents, using therapy-resistant lung tumor models.

Discussion

There has been both promise and failure in equal measure for chemoprevention of lung cancer. Numerous agents have been taken into clinical trials, and although many have not had any observable effects on lung cancer incidence, some have proven to be of harm. Dietary-derived agents offer great potential for use in chemoprevention regimens due to their favorable toxicity profiles and long history of use within the human populace. Curcumin, derived from the spice turmeric, has undergone extensive preclinical investigation in models of lung carcinogenesis, and so we sought to evaluate whether the evidence was sufficient to confidently apply this knowledge to clinical interventions with curcumin in lung cancer chemoprevention strategies.

In vitro studies (for both primary and tertiary chemoprevention) appear extremely limited in their choice of both model and concentration/dose selection. Mechanistic inferences are often made using a very limited choice of cell lines. This does little to represent the heterogeneity that is inherent in lung cancer, in which there are many distinct subclassifications with their own specific driver mutations, responding very differently to therapeutic intervention (Munoz et al., 2013). There is therefore a need to assess the effects of curcumin across more extensive cellular models. Such systems should include models of cellular resistance against the current individual and combinations of therapeutics used clinically; coculture approaches such as the organotypic model, which allows interaction of lung cancer cells with mesenchymal cells; and explant cultures using primary tissue and cell cultures from primary tissues. Use of such methodology would allow greater insight into the effects of curcumin across clinically relevant models of resistance, and would better take into account the interaction that tumor cells have with their microenvironment. Furthermore, explant cultures would allow short-term treatments of cells where the tumor architecture is maintained, and the use of primary tissue-derived cell lines would help to increase the heterogeneity of the sampling population. These approaches are now commonly used for investigation into molecular mechanisms for targeted agents, and should also be incorporated into preclinical strategies for chemopreventive agents. This would be a rational approach for improving the chances of translating observations of preclinical efficacy into the clinic.

A further issue for much of the in vitro data presented here is that of choice of dose. The extensive use of high concentrations of curcumin (>10 μM) to achieve positive effects on mechanistic endpoints is unlikely to provide meaningful insight regarding the potential in vivo mechanisms of action, particularly those that might relate to humans. Although high concentrations consistently induce apoptosis in lung cancer cell lines via mitochondrial-mediated mechanisms, there is little evidence to suggest that this can also occur with long-term exposure to low concentrations, which would bear greater relevance to clinical models of chemoprevention. To define the key mechanisms of curcumin's action that might translate to humans, it is essential to use clinically relevant systems and dosing regimens, but to date, little consideration has been given to these issues. Determination of suitable biomarkers of efficacy presents a problem for any chemoprevention trial, and translating in vitro markers of efficacy to the clinic could be deemed questionable, particularly when the models used have been so limited.

There are few animal models which accurately reflect the evolution of cancer in humans, and lung cancer models are no exception. The same limitations observed for the in vitro data apply to the animal models presented here, particularly in the tertiary models of prevention. The majority are mouse xenografts of Lewis lung carcinoma, or A549 cells, giving limited insight into potential drug efficacy across a wide and varied mutational spectrum. Orthotopic models of lung cancer in mice are less often used, but may present a more favorable system, particularly when assessment of drug delivery to tumors at their target site is required. If suitable orthotopic models cannot be generated, then patient-derived xenografts can provide well characterized models of specific gene mutations, which would greatly enhance investigation of preclinical drug efficacy (Zhang et al., 2013; Malaney et al., 2014). Although animal models of primary prevention are credible in that they deliver common environmental insults directly to the lung, there is still a paucity of data regarding efficacy of and mechanisms by which curcumin prevents lung injury. The anti-inflammatory effects of curcumin are most widely cited as its likely mechanism of action, but there are few comparators with commonly used steroidal/nonsteroidal anti-inflammatories with a similar mechanism of action. A wide variety of curcumin analogs and formulations designed to enhance absorption and/or retard metabolism have been used in in vivo models, most of which suggest enhanced antitumor efficacy compared with nonformulated curcumin, due to their greater bioavailability. Doses of curcumin used in vivo have the potential to be recapitulated in the clinical setting, and it may well be that curcumin formulated for greater bioavailability could be delivered orally at far lower doses than would be required for the parent compound. Although there is also promise of efficacy for the new curcumin analogs, their potential for clinical utility in a chemoprevention setting is limited until extensive and lengthy safety evaluations have been undertaken.

There are very few models of secondary lung cancer prevention, most likely due to the ambiguities as to whether early lesions definitively lead to carcinogenic progression. This is compounded by the rarity of resection of premalignant lesions, meaning that few tissues are available for use to generate cell lines to model this clinical paradigm. Furthermore, propagation of cells derived from such lesions will likely present with greater technical challenges compared with their malignant counterparts. Although a large proportion of the data presented here may show positive advocacy for the potential of curcumin in lung cancer prevention, there are a number of studies to note suggesting a detrimental role for curcumin in some in vivo models of lung cancer. Dance-Barnes et al. (2009) observed increased tumor multiplicity in a transgenic model of lung cancer [K-ras(G12C)], following administration of dietary curcumin. It has recently been shown that autophagy may promote BrafV600E-driven lung carcinogenesis (Strohecker and White, 2014), with curcumin known to be an inducer of autophagy in the lung (Xiao et al., 2013). Furthermore, in Lewis lung tumor xenografts, dietary curcumin increased the cross-sectional area of metastases concurrent with increases in levels of proinflammatory cytokines (Dance-Barnes et al., 2009; Yan, 2013). Curcumin is a potent antioxidant, yet paradoxically, antioxidants may have the facility to enhance carcinogenic progression (Sayin et al., 2014). However, it should be noted that, although trials

have shown higher lung cancer risk in participants taking β-carotene, this was not the case for those taking the similarly potent antioxidant α-tocopherol. Therefore, it is perhaps an unlikely prediction that all antioxidants would elicit procarcinogenic mechanisms in lung models (Kaiser, 2014). Mechanisms for the procarcinogenic antioxidant effect have been postulated to be due to decreased ROS, leading to downregulation of the ROS-induced activation of p53-regulated DNA damage response, although approximately 50% of all NSCLCs are p53 mutant (Mogi and Kuwano, 2011), which would discount this mechanism. Curcumin itself can undergo extensive oxidation, which functions as a pro-oxidant switch producing curcumin radicals (Heger et al., 2014), with potential for procarcinogenic oxidative damage. Despite these observations, much of the available evidence still favors curcumin as having anticarcinogenic potential in lung models. These ambiguities further highlight the absolute requirement that greater understanding of the pleiotropic properties of curcumin is required within the lung cancer chemoprevention setting.

Conclusion

Prior to large-scale chemoprevention trials being undertaken with curcumin, several factors need to be addressed. Here, we have reviewed the literature on efficacy data for curcumin in lung cancer, and stratified it according to which prevention model it could fit into. First, models for chemopreventive efficacy in the primary and tertiary setting are extremely limited and often inappropriate. Models are largely nonexistent for the secondary prevention setting. Second, most mechanistic data are obtained at curcumin concentrations that could never be achieved clinically, even when using formulations with greater bioavailability. Many models use cytotoxic endpoints only, but epigenetic modulation of carcinogenic pathways at subcytotoxic levels has had little consideration. The ultimate application of chemopreventive strategies is in the primary prevention setting. However, the tertiary chemoprevention setting provides a targeted, closely monitored cohort that has undergone extensive disease classification, allowing assessment of efficacy biomarkers to be correlated with progression-free and overall survival. This type of approach is necessitated, as the current lack of clinical efficacy data for curcumin in lung malignancy should preclude large-scale interventions within the healthy populace.

In summary, curcumin meets many of the criteria necessary to be successfully taken forward to the clinic, but there is much work still to be done to bridge the knowledge gaps prior to entering it into large-scale prevention studies for lung cancer. This is critical if the failings of other trials championing diet-derived agents are not to be repeated.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Howells, Mahale, Sale, McVeigh, Thomas, Steward, Brown.

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