Endotoxin and cancer

Endotoxina e câncer

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Abstract ***Exposure to endotoxin, a component of gram-negative bacterial cell walls, is widespread in many industrial settings and in the ambient environment. Heavy-exposure environments include livestock farms, cotton textile facilities, and saw mills. In this article, we review epidemiologic, clinical trial, and experimental studies pertinent to the hypothesis that endotoxin prevents cancer. Since the 1970s, epidemiologic studies of cotton textile and other endotoxin-exposed occupational groups have consistently demonstrated reduced lung cancer risks. Experimental animal toxicology research and some limited therapeutic trials in cancer patients offer additional support for an anticarcinogenic potential. The underlying biological mechanisms of anticarcinogenesis are not entirely understood but are thought to involve the recruitment and activation of immune cells and proinflammatory mediators (e.g., tumor necrosis factor α and interleukin-1 and -6). In view of the current state of knowledge, it would be premature to recommend endotoxin as a cancer-chemopreventive agent. However, further epidemiologic and experimental investigations that can clarify further dose-effect and exposure-timing relations could have substantial public health and basic biomedical benefits.***

Key words ***Cancer, Carcinogenesis, Endotoxin, Epidemiology, Lipopolysaccharide, LPS, Lung cancer, Occupational epidemiology***

Resumo ***A exposição à endotoxina, componente de paredes celulares bacterianas gram-negativas, é muito comum em plantas industriais e no meio ambiente. Ambientes de alta exposição incluem fazendas de criação de animais, instalações têxteis de algodão e moinhos. Neste artigo, revemos estudos experimentais, epidemiológicos e ensaios clínicos sobre a hipótese de que a endotoxina previne o câncer. Desde os anos 70, estudos epidemiológicos em têxteis de algodão e outros grupos ocupacionais expostos à endotoxina demonstram redução no risco de câncer de pulmão. Pesquisa experimental de toxicologia animal e ensaios terapêuticos limitados em pacientes com câncer dão suporte para um potencial anticarcinogênico. Os mecanismos biológicos anticarcinogênicos de base ainda não são completamente compreendidos, mas acredita-se que incluem recrutamento e ativação de células imunológicas e mediadores pró-inflamatórios (ex.: fator de necrose tumoral á e interleucina-1 e -6). Devido ao estágio atual de conhecimento, seria prematuro recomendar a endotoxina como agente quimiopreventivo. Porém, pesquisas epidemiológicas e experimentais que esclareçam relações de dosagem-efeito e exposição-relações temporais podem trazer benefícios para a saúde pública e a biomedicina básica.***

Palavras-chave ***Câncer, Carcinogênese, Endotoxina, Epidemiologia, Lipopolissacarídeo, LPS, Câncer de pulmão, Epidemiologia ocupacional***

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Endotoxins are integral components of the outer membrane of gram-negative bacteria cell walls, composed of proteins, lipids, and lipopolysaccharide (LPS), which are released when bacteria lyse[1]. LPS is considered to be responsible for most of the biological properties of bacterial endotoxins, particularly the lipid component (lipid A, a phosphoglycolipid)[2,3]. Endotoxins are a conta minant of various organic dusts and other environmen-tal media that support gram-negative bacte-rial growth[4-7]. The bacterial constituents are continuously shed into our surrounding environment; consequently, exposure to endotoxin is extremely widespread.

The ***Limulus*** amoebocyte lysate (LAL) assay for environmental endotoxin levels was adopted as the standard assay of endotoxin detection by the U.S. Food and Drug Administration in the 1980s[6]. This assay is based on the activation of a clotting enzyme in the lysate. Endotoxin levels are often expressed as endotoxin units (EU; 1 EU ≈ 0.1 ng, depending on the refer-ence standard), or as concentration of endotoxin per milligram of dust or per cubic meter of air. Of note, LAL tests are not internation-ally standardized, and measurements may vary among laboratories[6].

Of particular interest from a health effects perspective are the more intense exposures experienced in numerous manufacturing and agricultural settings throughout the world. Substantial endotoxin exposure occurs in agricultural work, garbage handling, sewage treatment, and incineration industries, textile industries (particularly cotton products factories), and saw mills, and to a lesser degree in occupations with exposures to certain types of water-based metal working fluids and in cigarette factories, fiberglass production facilities, and paper mills, among others[6,8-13]. Cotton factories in the Shanghai textile industry have been documented to have high endotoxin exposure concentrations[8]. By way of illustration, the mean of the endotoxin levels that have been measured in representative cotton factories was 366 EU/m3 (range, 44–1,871 EU/m3)[14]. Additionally, reported mean endo-toxin concentrations of 40 and 48 EU/m3 have been reported among municipal waste management workers[15,16]. In the agricultural industry, an overall mean endotoxin concentration of 230 EU/m3 has been reported, with mean measurements of 2,700 EU/m3 (range, 96–42,300 EU/m3) in the grain, seeds, and legume primary production sector and 1,190 EU/m3 (range, 62–8,120 EU/m3) in the primary animal production sector[15]. Other studies have reported endotoxin levels for livestock farmers ranging from 11 to 159 EU/m3 and field crop and fruit farming exposure levels ranging from low to > 1,500 EU/m3[12], and an exposure concentration of 140 EU/m3 among swine farmers[17].

Endotoxin is ubiquitous in the environment, although the exposure in occupational settings, frequently > 100 ng/m3, is more intense than exposure in the home, < 1 ng/m3[18]. Nonetheless, adverse health effects have been observed at endotoxin levels as low as 0.2 ng/m3[19]. The human health effects of acute exposure to endotoxin include sepsis; clinical symptoms such as fever, shaking chills, and septic shock; and, at lower doses, toxic pneumonitis, lung function decrements, and respiratory symptoms, such as byssinosis ("Monday morning chest tightness")[20,21]. Chronic exposures have been related to the risk of developing nonatopic chronic obstructive pulmonary diseases[19,22,23] and to the severity of asthma[24]. In contrast, numerous studies have demonstrated seemingly protective effects of environmental endotoxin exposure on atopic asthma risk and allergy development in early childhood[25,26], and atopy in adults[5,27,28]. As we discuss in some detail in this article, an inverse association with endotoxin exposure and the risk of cancer of the lung, and potentially other cancer end points, has consistently been demonstrated.

More than a century of clinical, laboratory, and epidemiologic research demonstrates that endotoxin has antitumor properties[29,30], but an understanding of the underlying mechanisms, and the subsequent development of an effective therapeutic application of endotoxin, has yet to be elucidated. We reviewed current and historical literature identified in Medline[31] electronic database, 1973-2008, using combinations of search key words such as endotoxin, LPS, epidemiology, lung, cancer, farmer, textile, and cotton. The text and citations of all identified supporting articles were reviewed with a particular focus on lung cancer, cotton textile workers [studies of textile workers that did not specify type of textile (i.e., cotton) were not reviewed], and studies of farmers by type of farming (dairy, crop, etc.). In addition a Medline search of publications from 1990 to 2008 was performed that reviewed the underlying mechanism of action so as to best describe the paradoxical understanding and association of the immune system response to endotoxin exposure and cancer.

In this review we discuss the historical and current understanding of the association of endotoxin exposure and cancer, therapeutic uses/treatment

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of cancer with LPS, epidemiologic studies of endotoxin exposure, and the underlying mechanisms to explain the human studies.

Endotoxin and cancer

Early experiments

In the late 19th century, William B. Coley, with the assistance of established anecdotal theories of the beneficial effect of fever on tumors[32], recognized regression and, in some cases, necrosis of tumors in advanced cancer patients suffering concomitant bacterial infections. Coley went on to successfully treat cancer in terminally ill patients by injecting mixed bacterial toxins in and around the tumors[33]. Despite the successes, this treatment was discontinued because the anticancer effect in patients was not consistent and repeated injections caused severe side effects, such as high fever and chills, that were not yet understood[34]. In the early 1940s, LPS was identified as the active ingredient in Coley's "bacterial vaccine", and the antitumor effects of the bacterial polysaccharide were successfully demonstrated ***in vivo***[35,36]. When isolated LPS was found to be ineffective as an antitumor agent in culture, it was determined that the effects were mediated by host-dependent mechanisms. Almost three decades later, tumor necrosis factor α (TNF-α) was determined to be the effective agent with antitumor properties[37]. By the mid-1980s therapeutic uses of TNF-α were being tested, but the therapy was less effective than hoped and caused undesired side effects, such as headache, nausea, vomiting, fever, hypotension, and diarrhea[34,38,39]. Around this same time, it was discovered that TNF-α was identical to cachectin, a mediator responsible for cachexia associated with sepsis[38,40]. The adverse effects of TNF-α were quickly accepted as limita tions to its direct use as an antitumor agent[34,40].

Treatment of cancer with LPS

Laboratory studies have successfully demonstrated therapeutic effects when administering LPS, or synthetic lipid A molecule, including inhibition of tumor size and growth[41-44]. Morita et al.[44] demonstrated this effect to be dose dependent. Additionally, an increased survival time has been noted for mice infected with cancer cells that have been inoculated with LPS[41,45]. An inverse dose-response association was demonstrated on the survival of cancer-bearing rats that were administered a synthetic analogue of lipid A[43]. Furthermore, antigenic memory has been demonstrated on mice with tumor cells planted intracranially; the mice with previous LPS-eradicated tumors showed increased survival compared with those without previous tumors[46].

Subsequently small clinical trials administering LPS, or a lipid A analog, have been performed. Cancer remission and disease stabilization have been demonstrated in cancer patients[47-50]. However, clinical toxicities have been unavoidable, even with the pretreatment of ibuprofen[47,48,50].

Epidemiologic studies of endotoxin exposure and cancer risk

Lung cancer

Cancer risks, particularly lung cancer, have been investigated in relation to occupational endotoxin exposures (Table 1). Cotton textile and farming industries have been a particular focus of epidemiologic research because of the substantial endotoxin exposure in these occupational settings, so we review these two industries in detail. Findings from early occupational cohort studies demonstrated reduced risks for lung cancer among cotton textile workers in the United States[51,52] and the United Kingdom[53], particularly in those with longer durations of employment. These results were regarded as somewhat surprising when first observed. Lower than expected lung cancer risks were subsequently reported from a cohort study conducted among women textile workers in Shanghai[8,54], a separate, unrelated, case-control study of both men and women in the cotton textile industry in Shanghai[55], cotton textile workers in Poland[56], and a study of Italian cotton mill workers[57]. Slightly elevated lung cancer risks were noted in Lithuanian and Finnish cohorts of cotton textile workers[10,58]; however, extended follow-up of the Lithuanian cohort, by 5 years, indicated significantly reduced lung cancer risk among male workers employed for at least 10 years[59], and the reported risk in the Finnish cohort was based on three cases. In a meta-analysis of studies of cotton workers published during or before 1990, and of studies published during or before 2002, lung cancer risk was significantly reduced[60]. Of note, the risk estimate for lung cancer was closer to unity when the more recent studies were included. The authors of the meta-analysis hypothesized this may be due to a lowering of dust concentration in the workplace in recent years.

Protection for lung cancer has been demonstrated to be similar among different types of

farming[61,62], although most studies reviewed demonstrated a greater protective effect in livestock farmers, specifically dairy farmers, compared with orchard/crop farmers[63-68]; Lange ***et al.***[64] demonstrated that the risk difference was statistically significant. Additionally, crop farmer exposures are predominantly during warmer harvest months (~ 4 months) and may not be representative of the actual annual dose, whereas the exposure experience of livestock farmers occurs 12 months a year[12,15,64]. For these reasons, and for simplification of discussion by selecting a homogeneous population, studies of dairy farmers are the focus of this review.

Inverse associations with respiratory cancers have consistently been observed among dairy farmers[63,66-71] (Table 1). In a cohort of Italian dairy farmers, an inverse association with increased number of dairy cattle on the farm was demonstrated; a significant inverse trend (p = 0.001) was reported for farmers with more recent exposures[66,69]. Lung and bronchus cancer risks were significantly lower among Finnish dairy farmers who continued farming at the time of follow-up (~ 20-year lag time) than for those that had quit farming, and risk of lung cancer was elevated for farmers who changed their production type to a crop or to beef cattle from the beginning of the study to follow-up, compared with those who continued as dairy farmers[63]. An earlier follow-up from this same Finnish Farm Register base cohort also demonstrated a significant decrease in lung and bronchus cancer mortalities among dairy farmers and reported the risk was lowest among farmers with at least 10 dairy cows[67]. Lung cancer mortality and incidence has also been shown to be significantly reduced in livestock farmers in the U.S. and Iceland, respectively[64,72].

Only limited epidemiologic evidence is available from investigations of lung cancer risks in nontextile and nonfarming occupations that entail endotoxin exposure, yet the findings are generally consistent with an anticarcinogenic effect.

Table 1. Lung cancer outcomes associated with occupational exposure to endotoxin.

Location	Study	Outcomes				
			Overall		Highest exposure	
		Sex	Nº of cases	RR (95% CI)	Nº of cases	RR (95% CI)
Cotton textile workers						
China	Astrakianakis ***et al.*** [8 a]	F	--	--	74	0.70 (0.52-0.95)
China	Levin ***et al.*** [55]	M, F	169	0.7 (0.6-0.9)	48	0.8 (0.5-1.3)
China	Wernli ***et al.*** [54 a]	F	641	0.8 (0.74-0.86)	236	0.72 (0.63-0.82)
Italy	Mastrangelo ***et al.*** [57]	M, F	36	1.03 (0.72-1.43)	10	0.93 (0.45-1.72)
Lithuania	Kuzmickiene and Stukonis [59]	M	70	0.94 (0.73-1.19)	2	0.24 (0.03-0.86)
		F	15	1.36 (0.76-2.25)	1	0.55 (0.01-3.08)
Poland	Szeszenia-Dabrowska ***et al.*** [56]	M	85	0.89 (0.71-1.10)	22	0.79 (0.50-1.20)
		F	12	0.55 (0.28-0.96)	9	0.82 (0.37-1.56)
UK	Hodgson and Jones [53]	M, F	42	0.76 (0.54-1.02)	--	--
USA	Henderson and Enterlina [51]	M	20	0.55 (-)	--	--
USA	Merchant and Ortmeyer [52]	M	18	0.74 (-)	3	0.52 (-)
Dairy farme's						
Finland	Laakkonen and Pukkala [63 b]	M, F	94	0.51 (0.42-0.62)	--	--
Finland	Pukkala and Notkola [67 b]	M	185	0.5 (0.4-0.5)	--	--
		F	14	0.5 (0.3-0.8)	--	--
Italy	Mastrangelo ***et al.*** [69]	M	75	0.64 (0.51-0.81)	7	0.47 (0.19-0.96)
NZ	Reit ***et al.*** [68]	M	--	0.66 (0.48-0.92)	--	--
USA	Stark et al. [70 c]	M	103	0.52 (-)	--	--
USA	Wang et al. [71 c]	F	21	0.33 (0.20-0.51)	--	--

Abbreviations: -- : data not available; F: female; M: male.
[a] Same cohort with different characterization of exposure; [b] Same base cohort with different years of follow-up; [c] cohort of farm residents; > 50% were dairy farmers.

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Reduced lung cancer risks have been observed in U.S. automotive workers exposed to endotoxin from water-based metalworking fluids[73]. The associations were primarily attributable to exposures within 10 years of death. Markedly reduced lung cancer incidence was also observed among pesticide applicators in the Agricultural Health Study cohort in the United States, which was attributed to a low prevalence of smoking habits[61,74]. Pesticides were the principal focus of that study; endotoxin has not yet been investigated as a possible explanatory factor for the lung cancer deficit. A deficit in lung cancer risk was also observed in a study of more than a million Finnish men based on their self-reported longest held occupation in the 1970 national census, lagged by 20 years, with endotoxin exposure determined by an occupational exposure matrix[75]; a deficit was not observed in women. In contrast, a study of occupational exposures in Leningrad Province, Russia, reported a > 2-fold greater risk of lung cancer in subjects ever occupationally exposed to cotton dust[76]. Of note, the risk estimate was based on six cases, and the evaluation of cumulative exposure to cotton dust in males resulted in a protective effect.

Among the studies of endotoxin exposure and lung cancer, quantitative estimates of historical endotoxin exposures have been reconstructed for the Lithuanian[59] and Shanghai[8,77] cohorts, and qualitative estimates of exposure have been estimated for Italian dairy farmers[69], to enable dose–response estimations of numerous site-specific cancers. All cohorts demonstrated a significant inverse dose response trend when evaluating endotoxin exposure by dust exposure category, cumulative cotton dust exposure, and number of dairy cattle on the farm, respectively, and lung cancer.

Other cancers

The findings to date for endotoxin exposure and risks for malignancies other than lung cancer have been limited and inconsistent. Much of the risk information on industrial exposures has been derived from the Shanghai cohort study of female textile workers. The first publication of this cohort described the occupational cancer risk for all textile workers, with select cancer outcomes evaluated by textile sector[54]. A decreased risk of most cancers was reported, with a significant decrease for esophageal, stomach, rectal, cervical, ovarian, and bladder cancers. Subsequent publications of this cohort evaluated the association of cumulative quantitative endotoxin exposure, as well as duration of occupational exposure classified by a job exposure matrix, and individual cancer end points, including liver, esophagus, stomach, rectum, pancreas, breast, brain, ovary, nasopharynx, and thyroid[78-86]. Notable findings from these studies include a decreased risk for cancer of the esophagus [hazard ratio (HR) = 0.5; 95% confidence interval (CI), 0.2–1.1] and increased risk for cancer of the nasopharynx (HR = 2.5; 95% CI, 1.1–5.4)[82,84].

Other cotton textile industry cohorts have been evaluated for the association of occupational endotoxin exposure and cancers other than the lung. Szeszenia-Dabrowska[56] reported a decreased risk of digestive cancers for men and women working in spinning and weaving departments. When considering individual cancers in men, there was a suggested increased risk of colon and liver cancers in weavers and stomach cancer in spinners, although these individual assessments were based on small numbers. Individual cancers in women showed a suggested decrease risk of rectal/anal and liver cancers and a suggested increase in gallbladder and ovarian cancers. In a Lithuanian cohort of textile workers, female workers in the spinning and weaving departments demonstrated increased risks for most individual cancers evaluated, with significant findings for breast and cervical cancers[10]. Other studies of cotton textile factory cohorts that defined exposure as employment in the production facility reported a decrease in breast and diges-tive cancers[51,53] and an increase in bladder, pharyngeal, and digestive cancers[51,57]. In a meta-analysis of 15 studies of cotton workers published during or before 1990, a nonsignificant increased risk of bladder cancer and decreased risk of digestive cancer were reported[60].

Among Finnish dairy farmers that con-tinued farming at the time of follow-up (~ 20-year lag time), the risks of colon, liver, breast, bladder, and skin cancers were significantly decreased, and risk of lip cancer was significantly increased[63]. Mastrangelo[69] reported a decreased risk of mortality associated with most cancers evaluated in a cohort of Italian dairy farmers, with a significant decrease in esophageal, pancreatic, and bladder cancers. In a cohort of predominantly dairy farmers, female and male, in New York State, a decrease in risk was reported for most cancers, with significant decreases in risk for colon/rectum and ovarian cancers in females and cancers of the oral cavity, large intestine, and bladder in males[70,71].

Physiologic response to endotoxin exposure and cancer risk

Various mechanistic argu-ments have been advanced regarding endo-toxin and carcinogenesis, focusing largely on complex interactions between the innate and adaptive immune systems[87,88]. Once internalized, LPS is bound by LPS-binding protein (LBP) and then transferred to CD14 protein (Figure 1). The CD14–LPS complex binds to and activates the Toll-like receptors (TLRs), which are cell membrane signaling proteins located on cell surfaces of macrophages and other cells. TLR4 is the predominant receptor for endotoxin and is required for endotoxin recognition[89]. Upon recognition of LPS, the innate inflammatory response is initiated and proinflammatory cytokines are released, including TNF-α, interleukin (IL)-1, and IL-6, which recruit immune cells to the site of exposure and induce the acute-phase response[3,88]. This host response is important for an effective immune system; however, overproduction of proinflammatory factors can cause endotoxic shock. In addition, TLR activation induces the expression of CD80 and CD86 on the surface of antigen-presenting cells that interact with the adaptive immune system to activate naive T-lymphocyte cells (T cells)[2,90,91]. The maturation of helper T cells (TH) results in cell-mediated (TH1) and humoral (TH2) subpopulations. The cytokines released by each of these cells have unique profiles and suppress the proliferation of the other subpopulation[88]. The immune reaction to LPS primarily activates TH1 cells, which maximize the killing efficiency of macrophages and induce up-regulation of proinflammatory mediators[90-92]. Notably, antitumor activity has been related to the cytokine profile associated with a TH1 response, whereas the TH2 profile has been shown to be ineffective in eradicating tumors[93,94].

Lung cancer

It has been postulated that bacterial endotoxin, through immunologic mechanisms, can be protective against lung cancer. Insofar as the route of endotoxin exposure is predominantly inhalation, the lung is one of the initial sites of immune stimulation[6]. Additionally, Klein ***et al.***[95] showed in a rat model that 5 min after injection of ***Escherichia coli***, the 20% of bacteria not taken up by the liver were found in the lungs, spleen, and blood. The TH1 response favored by LPS-activated immune cells may be a conjectured benefit to this initial site of exposure in that the TH1 immune response tends to be more localized than the TH2 response[88]. Moreover, the lung has been shown to produce or up-regulate the production of cofactors involved in the host response, including LBP, CD14, and TLR4, after LPS expo-

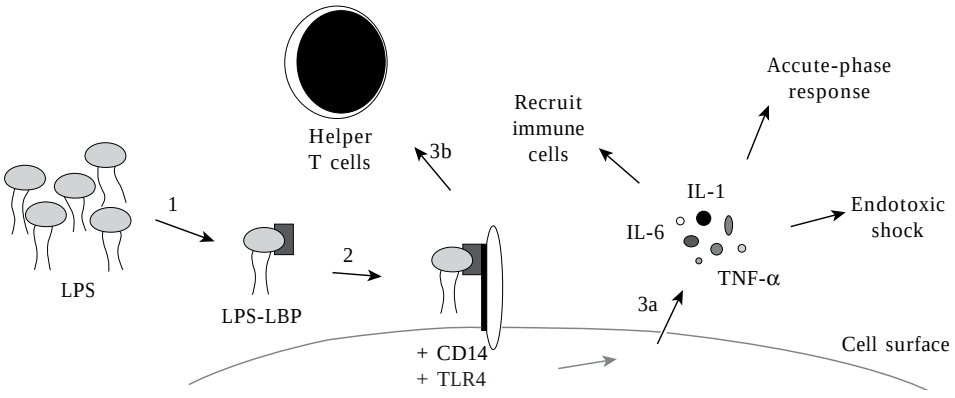

Figure 1. Mechanism of host response to LPS. Once internalized, LPS is bound by LBP (1) and transferred to CD14 (2); this new complex activates TLR4, followed by initiation of the innate (3a) and adaptive (3b) immune responses.

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sure[96-98]. It is generally accepted that LBP is produced in the liver, but it has been shown that significant levels of LBP could be produced elsewhere in the body under induced conditions, such as an inflammatory response[98]. In the presence of LBP, approximately 15-fold less LPS have been reported to be required to trigger an inflammatory response, as measured using TNF-α[99,100]. There is also consistent experimental evidence for an increase in TNF in the bronchoalveolar lavage (BAL) fluid in guinea pigs after cotton dust exposure[101], and an increase in TNF in the BAL fluid of humans after endotoxin exposure[102-104]. Likewise, Michel ***et al.***[105] reported a dose-dependent increase in TNF in the sputum of LPS-exposed subjects.

Other cancers

Other cancer end points have been studied, including cancers of the liver, esophagus, stomach, rectum, pancreas, breast, brain, ovary, thyroid, and nasopharynx, but not as extensively as the lung, and the findings have been inconsistent[10,51-54,56,57,70,71,75,78-81,83-86]. Nonetheless, subsequent effects in other organ systems are plausible because cells with TLR4 receptors are widely disseminated, and elevation of systemic inflammatory mediators, including TNF-α, IL-1, IL-6, and IL-8, has been shown after inhalation of LPS or media contaminated with endotoxin[2,3,105-109]. Additionally, a dose-related systemic response to inhaled LPS in human subjects after bronchial challenges with pure LPS has been demonstrated[105].

Discussion: future research needs

The individual immune response to endotoxin is a complicated result of dose, timing, poten-tial additive or synergistic effects, and geneti-cally determined responsiveness[29]. The health effects, including cancer outcomes associated with exposure, remain paradoxical.

Underlying biological mechanisms need to be elucidated

Insofar as endotoxin provokes an inflammatory response[105,106,108,110], it might reasonably be anticipated that inflammation would enhance, rather than prevent, carcinogenesis[111-113]. A sizable proportion of cancer deaths has been postulated to be attributable to infectious agents in which inflammation, mediated by recruitment of cytokines and growth factors to infected sites, may influence susceptibility to carcinogenesis through DNA damage and the simultaneous promotion of tissue destruction and repair[113]. The roles of ***H. pylori*** (which generates endotoxin) in the etiology of adenocarcinoma of the stomach, human papillomavirus in the etiology of anogenital carcinoma, and hepatitis B or C virus in hepatocellular carcinoma are cases in point[113-114]. Additionally, over-stimulation of inflammatory responses can lead to severe clinical symptoms, often termed sepsis, which can lead to progressive organ failure and death[115]. However, in lesser doses, which may relate best to chronic low-dose occupational and environmental endotoxin exposure, the proinflammatory mediators have been shown to inhibit tumor growth and retard tumor progression[37,116-118].

Exposure to LPS has been demon-strated to induce pathologic hyperactivity[119], but a mechanism of protection from this lethal reactivity, termed endotoxin tolerance, has been speculated. Endotoxin tolerance is the unresolved phenomenon defined as an altered capacity to respond to LPS activation immediately after a first exposure; that is, when exposed to continual small doses of LPS, the same TNF response of the initial exposure does not necessarily occur with subsequent exposure[48,50,105,109,120,121]. This tolerance has been shown to vary by dose as well as by length of time between treatments, and is theorized to allow the host more time to rid the pathogen[48,120]. Because this tolerance has been related to allowing a body system to endure continuous small doses without adverse symptoms, a better understanding of this mechanism may bring clarity to the relationships between endotoxin sensitivity (including acute toxic effects) and sepsis, and, possibly, between carcinogenesis and protection against cancer[120].

Epidemiologic corroboration

Experimental evidence from both animal models and therapeutic trials regarding the effects of endotoxin on carcinogenic processes has not been consistent[122,123], which indicates the importance of epidemiologic observations for guiding mechanistic and clinical research. Difficulties in studying endotoxin epidemiologically include the very large degree of exposure variability over time and among study subjects, and uncertainties in the measurement, or proxy measure, of exposure[124]. The general pattern of endotoxin exposure and cancer that emerges from existing epidemiologic research is one suggestive of an anticar-

cinogenic effect of endotoxin exposure that occurs in the lung and, perhaps, other organs. This consistency of findings has been main-tained when using job history as a proxy of exposure[51-54,57,59,63,64,70,71], incorporating a cumulative endotoxin exposure matrix variable[8,59,73], and using number of dairy cattle on the farm[69]. Nonetheless, with a few exceptions, most epidemiologic studies of endotoxin and cancer have not incorporated quantitative estimates of endotoxin exposure, which would strengthen causal arguments.

Although not unique to epidemiologic studies of endotoxin and cancer, absence of data on potentially confounding factors has been a limitation of most studies to date. Smoking status was incorporated in select analyses of endotoxin exposure and cancer and was shown to not account for the whole reduction in lung cancer risk, although the effect was exaggerated in those with low smoking habits[8,53,61,64,66,69]. Specifically, in the study of lung cancer among Shanghai textile workers, the inverse dose-response relation was not confounded by smoking, and importantly, the apparent protective effect was seen among both smokers and nonsmokers[8]. The very low prev-alence of smoking in this cohort of Chinese women workers precludes generalizability of these observations[54], thus underscoring the importance of obtaining pertinent data on smoking and other cancer risk factors in future research.

Concluding remarks

Exposure to endotoxin is ubiquitous in the environment at levels that have been shown to have physiologic effects and, in some instances, demonstrable health consequences. There is very consistent epidemiologic evidence that endotoxin is dose-related to risk reductions for lung cancer, and provocative evidence that risks for other cancers may be similarly reduced. Animal experimental research and limited therapeutic trial data are generally supportive of an anticarcinogenesis effect, and plausible biological mechanisms have been described. The public health implications of findings to date could be substantial. Nevertheless, a more extensive assessment of the role of endotoxin in the etiology of cancers of the lung and other organs is needed. Future epidemiologic and toxicologic research to elucidate more precisely dose-response relations and underlying mechanisms will need to be conducted before endotoxin, an agent with established noncancer toxic health effects, could be considered for widespread chemoprevention uses[125].

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