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Editorial

Inflammation, Infectious Burden and Cancer: an Epidemiological Paradox

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Inflammation and Cancer Incidence

There is considerable literature on fundamental studies on the connection between inflammation and cancer. Many cancers are believed to arise from sites of infection, chronic irritation and inflammation [1,2].

Epidemiological data [3-5], however, appear to be difficult to reconcile with these studies on the biology of inflammation and cancer [1.2]. In most developing countries such as India, populations are subjected to heavy infectious burdens owing to poverty, over-crowding, lack of sanitary facilities and hygienic environment, limited access (specially in the rural areas) to clean water, etc.; the evidence for this is infantile mortality at alarming rates [4]. The high rates of persistent infections should result in high levels of persistent, systemic inflammations. These inflammations would be further augmented by the ubiquitous presence of non-infectious (sterile) inflammogens arising from particulates in smoke released by cooking on fires fueled by burning cow-dung, wood, kerosene and coal, often in closed and unventilated tiny homes. Breathing these inflammogens, right from infancy, sets the stage for constant assaults from infectious and sterile inflammogens in most developing countries of Asia, Africa, and South and Central America [4].

When one examines the various areas of the world [3,4], one finds that countries assaulted by most inflammogens (i.e. the developing countries) show much lower incidence of cancer than the developed countries such as in North America, Scandinavia, Western Europe and Australia/New Zealand, despite the fact that their infectious burden is minimal and non-infectious inflammogens from cooking on smoky primitive fires do not exist. In other words, countries with high inflammatory load show lower cancer incidence and vice versa [3-5] contrary to the expectations from the molecular biology of inflammation and cancer [1,2]. No satisfactory resolution of this paradox has yet been proposed.

A typical case of this paradox is shown in Table I, where examples of high incidence of particular cancers in cities of USA, Switzerland, Canada and France are contrasted with the low incidence of cancers in various cities in India, after Bruce Alberts et al. [5]. The inflammation and cancer hypothesis [1,2] would predict the contrary trend, namely, since inflammation is more prevalent in India, cancer incidence should also be higher there. Actually, the epidemiological trend in Table I is shown by all other areas of the world [4,6]. In fact, the World Cancer Research Fund International (WCRFI) has clearly stated [6]: "Overall the age-standardized cancer rate(excluding non-melanoma skin cancer) is higher in more developed countries. There were 268 cases of cancer diagnosed in more developed regions compared to 148 in less-developed regions in 2012." [6].

Some Theoretical and Other Considerations

The fundamental biological approaches have been hinting at

the functional relationship between inflammation and cancer since 1863 [1]. Chronic inflammation, in common with the tissue injury and resultant inflammation, enhances cell proliferation. To quote Coussens and Werb [1]: "Although it is now clear that proliferation of cells alone does not cause cancer, sustained cell proliferation in an environment rich in inflammatory cells, growth factors, activated stroma, and DNA-damage-promoting agents certainly potentiates and/or promotes neoplastic risk." Again they [1] state: "In a sense tumors act as wounds that fail to heal." So, the biology of the relationship between inflammation and cancer is well established [1,2]. However, it does not fit with the epidemiological data [3-5], (Table I).

Table I. Incidence of some common cancers in India and in some Western countries (5).

	SITE OR ORIGIN OF CANCER	HIGH-INCIDENCE POPULATION		LOW-INCIDENCE POPULATION	
		LOCATION	INCIDENCE*	LOCATION	INCIDENCE*
(1)	Lung	USA (New Orleans, blacks)	110	India (Madras)	5.8
(2)	Colon	USA (Connecticut, whites)	34	India (Madras)	1.8
(3)	Bladder	Switzerland (Basel)	28	India (Nagpur)	1.7
(4)	Uterus	USA (San Francisco Bay Area, whites)	26	India (Nagpur)	1.2
(5)	Pancreas	USA (Los Angeles, Koreans)	16	India (Poona)	1.5
(6)	Kidney	Canada (NWT and Yukon)	15	India (Poona)	0.7
(7)	Oral cavity	France (Bas-Rhin)	14	India (Poona)	0.4
(8)	Leukemia	Canada (Ontario)	12	India (Nagpur)	2.2

* Incidence = number of new cases per year per 100,000 population, adjusted for standardized population age distribution (so as to eliminate effects due merely to differences of population age distribution). Figures for cancers of uterus are for women; other figures are for men (Adapted from Alberts, Bruce et al., THE CELL, Fourth Edition, Garland Science, New York (2003), p. 1327).

This is the Unresolved Paradox

With regard to Table I, it is pertinent to point out here some other factors. People in India extensively use turmeric in their food which has curcumin, a biphenol that has been shown to be a powerful anti-inflammatory and anti-cancer agent. Also, under-nourishment of most people in calories leads to the advantages of calorie-restriction (the new rising rich middle-class in India with abdominal obesity is excluded from this statement) that promotes less cancer. Since most people, especially in rural areas have to walk or bicycle several kilometers everyday, this exercise also promotes benefits similar to calorie restriction [2] in terms of less tendency to acquire cancer.

Conclusion

In conclusion, although the biological case for the relationship of inflammation with cancer is quite compelling, it is not compatible with the epidemiology of inflammogens and cancer incidence.

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