

Hypothetical Identification of Contra Distinct Human Lung Cancer Cell Lines as Natural Targets in Translational Research

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Abstract

Since the lung cancer cell (LCC) has direct access to the pulmonary vein, left heart and aorta, it has an optimum opportunity for distant dispersal. However, at necropsy, there are as many as ten dispersal patterns which are anomalous in terms of the hematogenous theory of metastasis. As such anomalies may imply imperfections in current concepts, the hematogenous route deserves comparison with its lymphogenous counterpart. On investigating the entire thoracic duct panoramically and the contralateral pulmonary blood vessels selectively, it was demonstrated that LCCs are more prone to necrosis in the blood stream than in the lymph stream. Therefore, it is hypothesized as follows: (a) that LCCs possess different intrinsic or acquired attributes during their transportation in blood and lymph, (b) that LCCs harvested from blood and from lymph will yield contradistinct cell lines when cultured, and (c) that such identifiable cell lines can become natural targets in translational research.

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Introduction

The functional morphology of lymph nodes can be traced with the footprints of the lung cancer cell (LCC) [1]. Therefore, what can their footprints in the circulating blood trace? LCCs entering the blood stream have optimum opportunities for distant dissemination. This is because they always have direct access to the pulmonary veins [2]. From these veins, they enter the left atrium and ventricle as well as the aorta whose branches feed every living tissue.

Like other authors, owing to expectations from such an enabling environment, Bryson [3] concluded that "blood-borne dissemination is the rule." However, he acknowledged that "the distribution is often somewhat anomalous."

Anomalous patterns

Anomalous distributions merit scientific investigation. Thus, as emphasized by Arnott [4] in the 1955 Harveian Oration, "Scientific principle requires us to be ever watchful for the unexpected and the anomalous." Therefore, this communication briefly draws attention to as many as ten anomalous topographical patterns of spread detected in lung cancer postmortem records as follows:

1. The nearer an organ is to the pulmonary primary, the more often it is invaded [5].
2. The invaded organs are generally limited in number, e.g., out of 8 listed organs examined in 6000 lung cancer autopsy records, only 2.6% contained secondary deposit in up to half of those organs [6].
3. The limitation may be so marked that only a solitary deposit is found on searching the whole corpse [7], e.g., surgeons confidently remove both the primary lung growth and its solitary brain deposit and thereby achieve many years of cure [8].
4. Bulky lung cancers, defined as those measuring over 10 cm across at autopsy, have myriads of opportunities for their cells to enter the blood vessels while attaining such an expanse and yet scarcely produce deposits outside the chest [9].
5. The rate of invasion of the lung situated just across the midline is only about 22% [10], despite the vascular interconnections assured through (a) the direct branches of the aorta, (b) the vena cava system, and (c) the vertebral venous plexus which Batson [11] described

epochally as having “free and rich anastomosis at each spinal segment.”

6. With regard to the invasion of both adrenal glands, their attribute of soil naturally remains constant while their attribute of site necessarily varies as to left- or right-sidedness as in a scientifically planned experiment [12] but the lack of symmetry in their colonization is not only statistically significant [13] but also pictorially poignant as in Figure 352 of volume 1 of Beattie, Dickson and Drennan’s “note the minute secondary growth in the opposite organ” [14].
7. One-sided preferential colonization may involve several organs in the one patient [7] e.g., Edinburgh Royal Infirmary Post Mortem No. 6/1946 in which a left lung cancer invaded the left frontal and parietal lobes of the brain, the left lobe of the liver, and the left adrenal gland.
8. Although the glomerulus is a uniquely known unit in terms of both its striking supply of arterial blood and the remarkable retardation of the supplied blood, yet its attack rate is only of the order of 1 per 2,000 [15].
9. LCCs may (a) surprisingly avoid several organs and (b) selectively attack just one organ, e.g., the adrenal gland [16] in which this peculiarity manifests still further by these cells sparing the ordinary parenchyma of the gland while attacking its already diseased adenomatous portion [17,18].
10. Even though the body’s widely distributed lymph nodes are richly supplied with arterial blood [19], yet their invasion pattern is not usually haphazard but harmoniously centrifugal [20].

Hypothesis

The above ten patterns recall the scientific principle that anomalies “may imply imperfections in our concepts and are often a stimulus to discovery” [4]. If discovery is to materialize in the instant quandary, perhaps these ten patterns are best viewed from the perspective that the ascendant acceptance of blood-borne dissemination is imperfect. If that be the position, comparisons between lymph and the blood pathways are warranted.

This was achieved with a double barreled study of the thoracic duct and pulmonary blood vessels. The duct was (a) obtained in continuity by using a special postmortem technique [21], (b) coiled up in Swissroll manner, (c) processed in one block, (d) cut with the sledge microtome in one plane, and (e) stained with haematoxylin and eosin on one slide [22]. This method yielded a panoramic view of how LCCs fare in lymph itself among red cells which tend to cluster in the cul-de-sacs formed by its valves. It

was discovered that LCCs appear more necrotic in the midst of the red cells than in the lymph proper. Moreover, the concomitant study of blood vessels in one-inch square blocks taken from the base of the contralateral lung revealed the same proneness to necrosis that is attributable to hematogenous factors [22]. It was concluded, therefore, that a more checkered existence is the fate of LCCs in circulating blood vis-à-vis the lymph stream [23].

Discussion

The above pathologic overview underpins the working hypothesis that, owing to the possession of intrinsic or acquired attributes, there are two identifiable contra distinct types of LCCs, namely, the blood-borne and the lymph-borne. Admittedly, this conclusion may be questioned on the ground that the delineated anomalous patterns are not the rule but the exception. If so, the answer lies in the importance of exceptions! “Often,” as my Glasgow teacher argued [24], “an imperfect performance reveals the intricacy of a dance more clearly than the most polished execution.” For, as he added, “Not infrequently normal biological processes are first elucidated by a study of the abnormal.”

Accordingly, even if seemingly, the abnormal ten patterns teach a lesson which may be examined in the light of the new endeavors in the field of gene research. For instance, workers at Houston’s MD Anderson Cancer Center established a retroviral vector-mediated system in order to allow efficient transduction of the wild-type p53 gene into human lung cancer cell lines H356a and H322a [25]. Another American group [26] analyzed the effect of wild-type p53 transfection on the growth potential of a human lung cancer cell line (Hut292DM) that expresses endogenous wild-type p53. Similarly, in a combined US-Japanese research [27], normal or mutant p53 CDNAs were introduced into a lung cancer cell line (NCI-H358) with a homozygous deletion of p53 which expresses no p53 mRNA or protein.

Clearly, these researches on human lung cancer cell lines confirm the view that p53 is the cellular gatekeeper for growth and division [28]. Hence, what does the present paper point to?

It points to the need for expressly slanting the new endeavors towards two contra distinct human lung cancer cell lines which should be derived from parent cells harvested from arterial blood as well as from lymph drawn from the thoracic duct whose cannulation has become a relatively practical procedure [29].

Conclusion

Long ago [30], I reviewed the patterns of metastasis in lung cancer. In the present paper, the scope has been widened by slanting the work toward the benefits that may accrue from lymph- and blood-related gene researches. In all probability, any discovery made in this limited sphere will be bolstered in Translational Laboratories [31], and maximized through drug development [32].

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