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Original Research

A filter-flow perspective of haematogenous metastasis offers a non-genetic paradigm for personalised cancer therapy

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Abstract Research into mechanisms of haematogenous metastasis has largely become genetic in focus, attempting to understand the molecular basis of 'seed–soil' relationships. Preceding this biological mechanism is the physical process of dissemination of circulating tumour cells (CTCs) in the circulation. Patterns of metastatic spread have been previously quantified using the metastatic efficiency index, a measure quantifying metastatic incidence for a given primary-target organ pair and the relative blood flow between them. We extend this concept to take into account the reduction in CTCs which occurs in organ capillary beds connected by a realistic vascular network topology. Application to a dataset of metastatic incidence reveals that metastatic patterns depend strongly on assumptions about the existence and location of micrometastatic disease which governs CTC dynamics on the network, something which has heretofore not been considered – an oversight which precludes our ability to predict metastatic patterns in individual patients.

1. Introduction

Nearly 150 years after Ashworth's discovery of the circulating tumour cell (CTC) [1], the putative vector of haematogenous metastatic disease, the mechanisms driving this process remain poorly understood and unstoppable [2]. For over a century the dominant

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paradigm has been the seminal, yet qualitative, seed–soil hypothesis proposed by Paget in 1889 [3]. This idea was challenged by the 'mechanical hypothesis' put forward by Ewing in the 1920s [4], that postulated that metastatic incidence is due to differential blood flow. These two opposing views were merged in 1992, when a quantification of the contribution of mechanical and seed–soil effects was attempted by Weiss [5], who considered the 'metastatic efficiency index' (MEI) of individual primary tumours and metastatic sites [6] (see Fig. 1A). The MEI captures the compound inefficiency of all processes acting between the cancer cells leaving the primary tumour and forming clinically detectable metastases. He calculated MEI as the ratio of metastatic involvement to blood flow through an organ and three classes of organ pairs emerged: low, where the soil–organ relationship is hostile; high, where it is friendly and medium, where blood flow patterns to a large extent explain patterns of metastatic spread.

The utility of Weiss' classification method largely ended there, and has since been put aside in favour of genetic investigations [7], an exception being work in prostate cancer by Pienta and Loberg [8] showing a lack of correlation between blood flow and incidence, suggesting strong seed–soil effects. While illuminating, the gene-centric approach to understanding patterns of metastatic spread has yet to offer any actionable conclusions, and its applicability is threatened by the growing understanding that genetic heterogeneity, not clonality, is the rule in cancer [9,10]. Our aim is to revisit the pre-genetic model and show that a physical perspective of metastatic spread can lead to new and actionable insights into this enigmatic disease process.

While primary tumour and lymph node metastases are carefully described in the clinic, metastatic disease is considered to be a binary change of state, a patient being diagnosed either with or without metastasis, M0 or M1. Until recently, this was appropriate, as even perfect information about the existence and distribution of metastatic disease would have done little to affect treatment choice, the options being limited to the use of systemic chemotherapies. Recent years, however, have witnessed the advent of more effective and tolerable localised therapies for metastatic involvement, in the form of liver-directed therapy [11], bone-seeking radionuclides [12] and stereotactic body radiation therapy [13]. These recently adopted modalities have allowed for targeted therapy to specific parts of the body with minimal side-effects and high eradication potential. Further, trials offering treatment with curative intent to patients with limited, 'oligometastatic' disease have shown promise [13], although it is not yet possible to identify such patients in an objective manner [14]. The time is therefore ripe for a quantitative framework that can analyse and guide these and similar efforts.

In this paper we apply a recently published framework for understanding haematogeneous metastates [15,16] to an existing dataset of metastatic spread [17] in an attempt to draw new conclusions and suggest novel therapeutic options (see Fig. 2). Specifically we

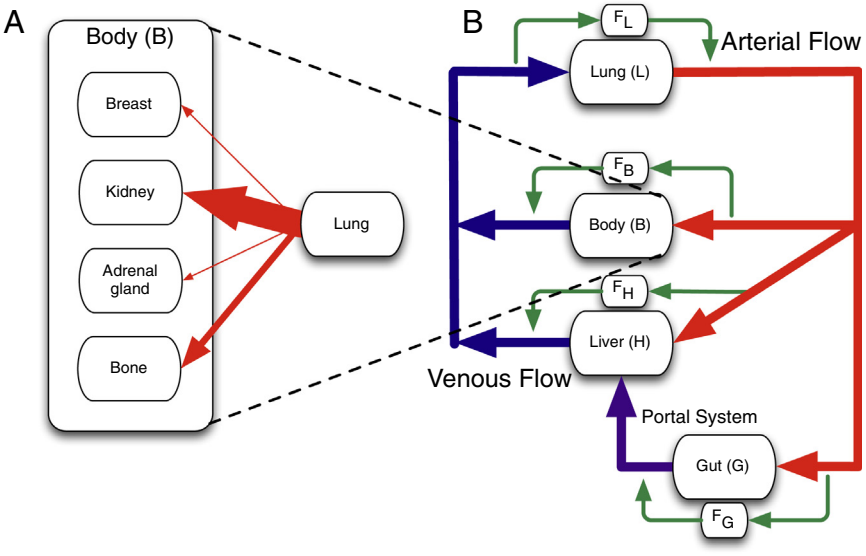

Fig. 1. Schematic of (A) Weiss conceptual framework for calculating the metastatic efficiency index (MEI) and (B) our extension of the framework. (A) Weiss used the relative arterial blood flow to normalise the metastatic incidence and calculate the MEI (the width of the arrows is proportional to blood flow). (B) In our framework we consider both relative arterial blood flow and venous flow. This forces us to consider the loss of circulating tumour cells (CTCs) that occurs in capillary beds of different organs. It is evident by inspection of the network diagram that tumours originating in the gut and lung experience significantly different flow patterns and a different order in which they experience filtration at capillary beds than tumours originating in other parts of the 'body' [15]. The alternate pathways (green) represent the fraction of cells which evade arrest (filtration) at a given capillary bed. There are scant measurements of this fraction in the literature, and none in clinical studies that evaluate outcomes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)