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CORRESPONDENCE

Invasion and metastasis: the elusive hallmark of cancer

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In their seminal review published nearly two decades ago, Hanahan and Weinberg introduced the "hallmarks of cancer" and typified essential biological abilities that are acquired by human cancer [1], including sustained proliferative signaling, resistance to apoptosis, evading growth suppressors, induction of angiogenesis, enabling replicative immortality, and invasion and metastasis. Eleven years later, in 2011, the authors added two more emerging hallmarks, reprogramming of energy metabolism and evading immune destruction [2]. In their updated review, genomic instability and tumor-promoting inflammation were also added as enabling characteristics of tumorigenesis. Since then, several authors attempted to define the complexities of cancer biology in different ways and challenged the criteria for inclusion of specific hallmarks [3].

Metastatic dissemination of malignant cells is the main cause of cancer-related mortality. Metastasis is one of the most enigmatic features of cancer biology, and is a complex sequential and interrelated process leading to the formation of distant secondary tumors, collectively termed the invasion-metastasis cascade. The series of events is initiated by migration and local invasion of cells into the surrounding extracellular matrix. Subsequently, cells intravasate into the vasculature, survive the rigorous conditions within the bloodstream, arrest at distant sites, extravasate into the organ parenchyma, adapt to the new microenvironment to form dormant cells or multicellular micrometastases, and eventually thrive in the foreign milieu to establish clinically detectable macroscopic metastases [2].

Growing understanding of hallmark principles leading to metastasis has assisted knowledge-based therapeutic development; however, despite the rapidly growing armamentarium of targeted therapeutics (so-called magic bullets), enduring disease-free responses for most forms of cancer are rare, and cures are even rarer [4]. Unless detected early and surgically excised, targeting specific hallmark capabilities is only transiently effective. Eventually, resistance emerges due to the adaptive and evasive resistance strategies developed by cancer, enabling tumor progression, often with renewed vigor. Successful invasion and metastasis depend on all the other acquired hallmark capabilities [1] to which different strategic approaches have been developed [4].

However, the bigger question remains: what is the most critical hallmark of cancer? In his essay [5], Lazebnik pointed out that except for invasion and metastasis, all five of the six original hallmarks are shared by both benign and malignant tumors, and are therefore rather indistinctive of "cancer". This concept can be similarly expanded to the updated hallmarks—metabolic reprogramming, genomic instability, tumor-promoting inflammation and immune evasion, which also prevails in benign tumors [6–10]. An exception to this is endometriosis, a prevalent benign condition among females, in which endometrial cells spread and invade distant sites [3]. Excluding this one or possibly other few exceptions, invasion and metastatic dissemination are not characteristic of benign conditions. We would therefore argue that the importance of the invasion and metastasis hallmark derives from the most defining feature of malignancy, which entails the ability to invade, to spread, and to colonize distant tissues. Unfortunately, no approved drugs have been specifically designed to block invasion or metastasis, and instead current therapeutic approaches aim at reducing tumor cell viability by targeting the other hallmarks.

While the hallmarks model presents an excellent depiction of what goes wrong in cancer cells, it does not answer the question of what is the hierarchy of the hallmarks in the broader perspective of therapeutic strategies. Here, we propose a modified hallmarks model, in which invasion and metastasis is shifted to the center of attention (Fig. 1),

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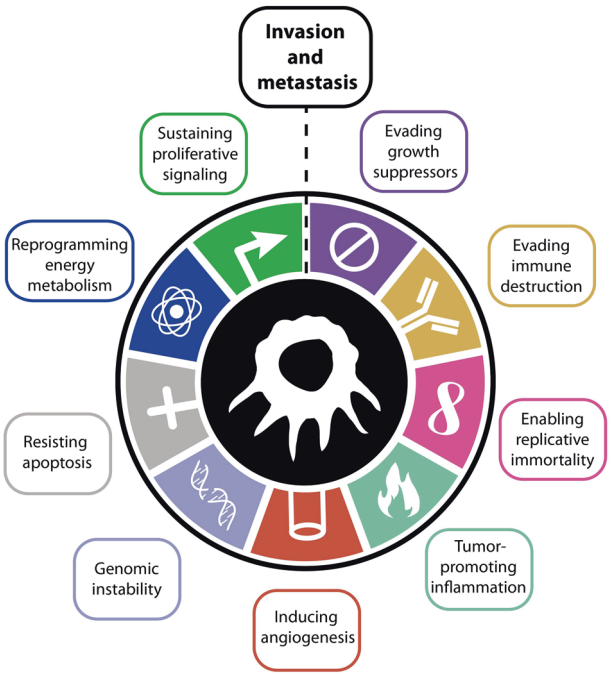

Fig. 1 Invasion- and metastasis-focused hallmarks of cancer. Illustration of the hallmarks of cancer with the invasion and metastasis hallmark advanced to the center of the model, to emphasize its superior role in malignancy

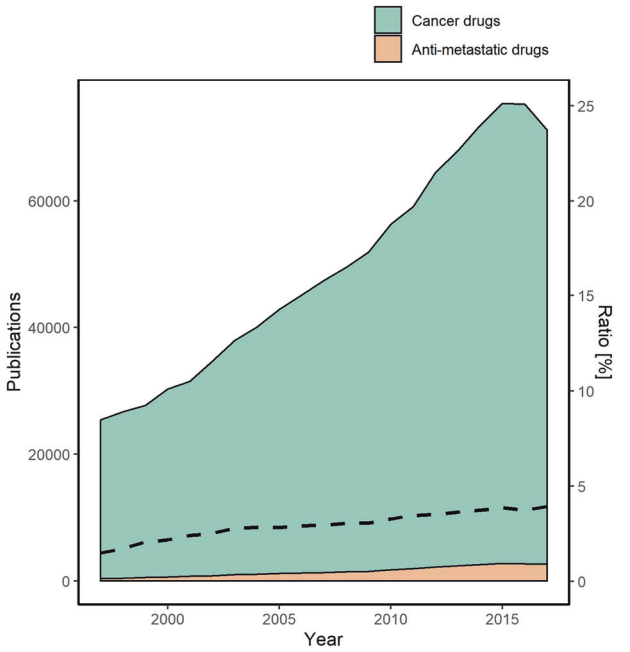

Fig. 2 Annual publications associated with antimetastatic drugs. Total annual publications among cancer-related research in the years 1997−2017 as obtained by Pubmed search. The search query used to retrieve drugs-associated publications was: "Drug" | "Drugs" | "Treatment" | "Treatments" | "Therapy" | "Therapies". The search query used to retrieve antimetastatic-associated publications was: ("Anti metastatic" | "Antimetastatic" | "Anti metastasis" | "anti-metastasis" | "Anti invasive" | "Anti invasion" | "Anti migratory" | "Anti migration" | "Anti degradation" | "Antiproteolytic" | "Anti proteolysis" | "Anti MMP" | "Anti matrix metalloproteinase" | "Metastasis prevention" | "metastatic prevention" | "Anti invadopodia") OR ("Invasion" | "Invadopodia" | "Migration" | "Degradation" | "Proteolysis" | "Proteolytic" | "MMP" | "Matrix metalloproteinase") AND ("Inhibitor" | "Inhibitors" | "Antagonist" | "Antagonists"). The ratio between the queries is represented by a dashed line

thereby emphasizing it as a potentially superior therapeutic target. Since therapies aiming at most of the other hallmark-specific mechanisms affect cell viability directly, the population of cancer cells is subject to inevitable selection and Darwinian evolution. Conversely, blocking invasion does not directly affect cell survival, and thus imposition of a selective pressure towards new resistant lineages is less likely [11]. Furthermore, blocking the metastatic cascade may prevent seeding and subsequent unrestrained exponential growth of unlimited number of distant metastatic colonies; therefore, we would argue that anti-invasive therapy may be considered an efficient tumor suppressing and "cytotoxic" treatment without even killing a single tumor cell.

Metastatic dissemination is responsible for most cancer mortalities, yet its prevention per se receives very little attention in the literature as opposed to treating primary tumors or secondary lesions. We have previously mentioned that most clinical investigation is not focused on invasion-related outcomes, and instead, medical research is predominantly focused on other objectives such as disease progression and tumor shrinkage [11]. Indeed, literature search for publications associated with metastasis prevention with antimetastatic drugs, out of all publications associated with cancer therapy, revealed that only a minor fraction (<4%) of publications is associated with metastatic prevention therapy, indicating that most publications in cancer therapy focus on the other hallmarks of cancer (Fig. 2).

Despite efforts being made by various groups [12–18], the extraordinarily little weight given to antimetastasis therapeutics raises a cause of concern. These observations advocate the need to prioritize hallmark-based efforts and therapeutics targeting differently, as proposed in Fig. 1, centering one's attention on metastasis. Along these lines, since most successful treatments rely on early detection and surgical excision to prevent future tumor dissemination, arguably, metastatic-preventive care where the invasive phenotype is completely blocked could be just as successful.

Other studies have referred to the misrepresentation of invasion and metastasis [12, 19]; however, to our knowledge, we are the first to evaluate it objectively in the literature. This analysis, therefore, highlights the dissociation between the well-accepted and unparalleled role of invasion and metastasis in cancer mortality and the paradoxical underrepresentation of research devoted to its prevention. This apparent contradiction could be explained by the chronology of the metastatic cascade whereby metastases would not develop without a

primary tumor; the intuitive association between growth and spread that do not necessarily coincide and lead to profoundly different clinical implications; and the misconception that killing cancer cells and metastatic lesions are synonymous with preventing metastasis [19, 20]. Therefore, the proposed hierarchical model attempts to advance towards reconciliation of this contradiction.

The hallmarks of cancer were proposed as a master plan to guide research efforts that aim to understand the core traits of cancer and derive treatments for this exceptionally complex disease. One of the most persistent challenges in cancer treatment involves the countervailing emergence of advanced patterns of resistance that gradually overcome existing and novel therapies. This challenge may be circumvented by shifting research focus and treatment paradigms towards blocking the invasion and metastasis hallmark, which serves as a natural candidate for the most important and defining trait of malignancy. However, while we are immensely engaged in using a continuously growing arsenal of strategies for disrupting cancer viability, we may easily miss the most critical and elusive property of them all.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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