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An agent-based modeling framework linking inflammation and cancer using evolutionary principles: Description of a generative hierarchy for the hallmarks of cancer and developing a bridge between mechanism and epidemiological data

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ABSTRACT

Inflammation plays a critical role in the development and progression of cancer, evident in multiple patient populations manifesting increased, non-resolving inflammation, such as inflammatory bowel disease, viral hepatitis and obesity. Given the complexity of both the inflammatory response and the process of oncogenesis, we utilize principles from the field of Translational Systems Biology to bridge the gap between basic mechanistic knowledge and clinical/epidemiologic data by integrating inflammation and oncogenesis within an agent-based model, the Inflammation and Cancer Agent-based Model (ICABM). The ICABM utilizes two previously published and clinically/epidemiologically validated mechanistic models to demonstrate the role of an increased inflammatory milieu on oncogenesis. Development of the ICABM required the creation of a generative hierarchy of the basic hallmarks of cancer to provide a foundation to ground the plethora of molecular and pathway components currently being studied. The ordering schema emphasizes the essential role of a fitness/selection frame shift to sub-organismal evolution as a basic property of cancer, where the generation of genetic instability as a negative effect for multicellular eukaryotic organisms represents the restoration of genetic plasticity used as an adaptive strategy by colonies of prokaryotic unicellular organisms. Simulations with the ICABM demonstrate that inflammation provides a functional environmental context that drives the shift to sub-organismal evolution, where increasingly inflammatory environments led to increasingly damaged genomes in microtumors (tumors below clinical detection size) and cancers. The flexibility of this platform readily facilitates tailoring the ICABM to specific cancers, their associated mechanisms and available epidemiological data. One clinical example of an epidemiological finding that could be investigated with this platform is the increased incidence of triple negative breast cancers in the premenopausal African–American population, which has been identified as having up-regulated of markers of inflammation. The fundamental nature of the ICABM suggests its usefulness as a base platform upon which additional molecular detail could be added as needed.

1. Introduction

There is an increasing awareness of a fundamental link between inflammation and cancer, with compelling epidemiological and mechanistic information to support this association [1–5]. Infectious diseases that lead to chronic, non-resolving inflammation, such as Hepatitis B and C, and Human Papilloma Virus, are known to promote the development of cancer [1–3]. Conditions associated with a chronic and recurring disordered inflammation, such as ulcerative colitis and primary sclerosing cholangitis, are well known to predispose to cancer [1–3]. Obesity, which is increasingly recognized as a metabolically induced persistent inflammatory state, is associated with an overall increase in cancer incidence [1]. More recently, host–microbe interactions have been invoked as being a crucial factor in promoting an individual's inflammatory state and correspondingly driving cancer risk [2,3]. Furthermore, pharmacological interventions that result in general suppression/reduction of inflammation, such as aspirin, have been demonstrated to reduce overall cancer incidence [6,7].

However, inflammation is such a protean and basic biological process that attempts to identify mechanistic links between inflammation and oncogenesis return a plethora of concurrent, parallel and

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ambiguous interactions [1–5]. For instance, the role of inflammation in cancer development and progression has been divided into two distinct, contradictory roles: a negative role in promoting the generation of genetic instability that can lead to cancer [8] and a positive role in being able to defend against invasion of the developed tumor [9]. However, this Janus-faced view of inflammation is not limited to its role in cancer development and progression; rather it is a fundamental property of the intersection between inflammation and disease [10,11]. Translational Systems Biology (TSB), which is the use of dynamic computational modeling to bridge the gap between mechanistic knowledge generated at the basic science level and observations and data generated at the clinical and population level, was initially developed to examine the protean and paradoxical nature of inflammation [12]; we now apply the concepts of TSB to the study of the intersection between inflammation and cancer.

We turn to the issue of oncogenesis and the subsequent behavior of developed cancers. Hanahan and Weinberg have previously listed six hallmarks of cancer: (1) Sustaining proliferative signaling, (2) Evading growth suppression, (3) Resisting cell death, (4) Enabling replicative immortality, (5) Activating invasion and metastases and (6) Inducing angiogenesis [5,13]. These factors can be further grouped into those concerning intrinsic properties of cancer cells, resulting from a fundamental change in their internal programming (Hallmarks 1–4) and those related to a macrophenomenon associated with a population of cancer cells, i.e. the tumor (Hallmarks 5 and 6) [1]. We further refine this categorization by establishing a hierarchy of functional relationships and generative dependencies between these properties to better identify fundamental driving principles in oncogenesis (see Fig. 1):

1st Order Process: Promotion of Genetic instability/plasticity. This process refers to genetic damage, manifest as DNA base pair alterations, that accumulates for each individual cell. When the genetic damage is greater than the cell's repair/response capabilities, this damage can propagate generationally as the damaged cell divides. Note that this process represents changes in the DNA sequence, and not just the regulation of the gene expression network. Therefore, alterations due to gene instability/plasticity represent a more fundamental disturbance to the function of a gene than epigenetic or signaling/regulatory alterations.

2nd Order Process: Functional Deficits manifesting at the individual cell level. These functional properties reflected in the behavior of individual cells fall into the general category of Hallmarks 1–4: promoting proliferation (either stimulating proliferation or loss of proliferation suppression), loss of mortality (dysfunction of telomerase, impairment of apoptosis), impaired damage repair (leading to increased genotypic plasticity), loss of migration inhibition (leading to failure of multicellular tissue ordering/structure and acquisition of invasiveness, as seen resulting from epithelial–mesenchymal transition). These are the functional consequences of the genetic disturbances happening at the 1st Order level, and constitute the loss of evolutionarily generated control structures required to maintain the integrity of multicellular organisms. The loss of these control functions represents a shift of active and relevant evolutionary fitness/selection from the entire organism to a sub-organismal level (see Discussion).

3rd Order Process: Multicellular effects evident in the behavior of the tumors as a population of cells. These properties generally correlate to Hallmarks 5 and 6, and include: promoting angiogenesis, interactions with the stromal microenvironment, immune evasion, and release of potentially metastatic cells Signaling events between tumor cells and surrounding normal tissue primarily drive these processes. Because they represent feedback between the tumor and normal tissue, many of these interactions represent hijacking of "normal" processes present in multicellular organisms, i.e. angiogenesis, tissue healing, prevention of anti-self immune responses.

The significance of this categorization structure is that lower order processes drive and generate the higher order processes. For instance, 2nd Order functional abnormalities result from 1st Order disturbances that disrupt genetic control structures; 3rd Order processes result from the intersection between disordered cells manifesting 2nd Order abnormalities. Therefore, focusing initial

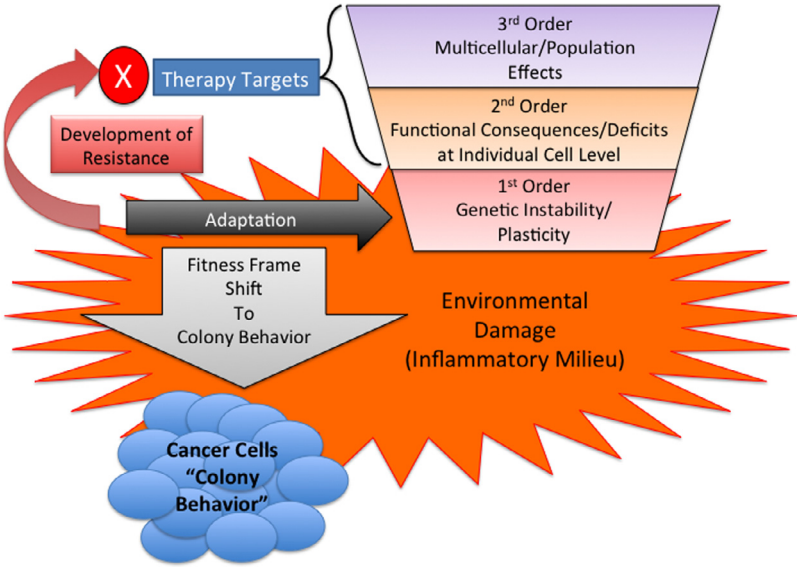

Fig. 1. The Generative Hierarchy for Cancer and the Effect of Inflammation. The Generative Hierarchy for cancer is depicted as an inverted trapezoid to reflect its process dependencies, and demonstrates how inflammation fosters a shift in the frame of evolutionary fitness and its impact on development of resistance to therapy. Inflammatory damage most heavily influences the 1st Order processes by fostering DNA-damage. While higher order effects of inflammation may be present (2nd Order signaling to increase proliferation, 3rd Order microenvironmental cues to promote angiogenesis), these processes are ultimately driven by cancer cells subjected to 1st Order disturbance (damage DNA/mutations). The increase in genetic instability/plasticity is manifest as adaptation at the 1st Order level, reflecting a shift to sub-organismal, prokaryote-like colony adaptive behavior. This accelerated adaptive cycle promotes the tumor's development of resistance to therapeutic interventions, regardless of where in the Generative Hierarchy they are targeting the tumor.