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Cancer is a propagandist

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ABSTRACT

Communication among cells (also known as cross-talk) plays a prominent role in the current knowledge of the pathophysiology of cancer and of cancer-associated conditions such as paraneoplastic syndromes and cachexia that are responsible for much of cancer's morbidity and mortality. Yet, biomedical scientists lack an explicit unifying frame that places this exchange of molecular information at the core of their understanding of cancer as a systemic disease. Propaganda is a type of information that aims at misleading, a form of communication intended primarily to serve the messenger. The biased molecular cross-talk between cancer and non-cancer cells can be considered as a form of biological propaganda. I here propose CANCER IS A PROPAGANDIST as a metaphor that may serve as a unifying frame to interpret both cancer and cancer-associated syndromes under the same communication-based concept and may thus serve to bring together research that is currently compartmentalized under separate disciplines.

1. Introduction

Communication among cells, in the form of a constant exchange of molecular information usually defined as cross-talk, plays a prominent role in the current scientific understanding of cancer's pathophyisology. Molecular information exchanged between cancer and non-cancer cells can take the form of growth and angiogenic factors, hormones and peptides, cytokines and other inflammatory molecules, antibodies and other immune-related proteins, metabolites, nutrients, exosomes and other forms of microvesicles, and many more (Balkwill & Mantovani, 2012; Hanahan & Coussens, 2012; Hanahan & Weinberg, 2011; Kuzet & Gaggioli, 2016; Liu & Cao, 2016; Vander Heiden, 2011). Indeed, cross-talk between cancer cells and the stroma, or microenvironment, features prominently in the depiction of the mechanisms of most of the recognized cancer hallmarks, including proliferation, survival, invasion, metastasis, angiogenesis, inflammation, evasion of immunity, and altered energetics (Hanahan & Coussens, 2012; Hanahan & Weinberg, 2011). An exchange of molecular information is also an essential component in the explanation of mechanisms leading to development of paraneoplastic syndromes and of cancer cachexia, conditions in which the cancer macroenvironment, i.e., the whole body, is involved in the cross-talk (Al-Zoughbi et al., 2014; Ali & Garcia, 2014; Falanga, Schieppati, & Russo, 2015; Laviano & Molfino, 2016). Although paraneoplastic syndromes and cachexia are directly responsible for much of cancer's morbidity and mortality, they are in large part studied separately from the biology of cancer cells proper (Utech, Tadros, Hayes, & Garcia, 2012). Despite the widely accepted recognition of the essential role of intercellular communication in the mechanisms of cancer and its associated syndromes, the scientific community lacks an explicit, overarching, unifying frame for this concept.

2. Metaphors in biomedical science

Metaphors are powerful tools humans use to make sense of the world. Scientists use metaphors to make sense of complex scientific issues. In addition to their important role in helping our minds grasp abstract concepts, science metaphors often end up shaping the direction of scientific research. The fields of immunology and of cell death provide two examples of the power of metaphors in biomedical science. Immunologists have used the SELF/NONSELF metaphor as an essential tool to conceptualize the immune system, while that same metaphor has itself fundamentally shaped the direction of research in immunology over decades (De Donato Rodriguez & Arroyo-Sanros, 2011; Tauber, 2017). In the field of cell death, the metaphorical concept of ALTRUISTIC CELL SUICIDE has been instrumental in conceptualizing, directing and popularizing an area of research that was initially considered at best unglamorous when not utterly useless (Fantuzzi, 2016; Reynolds, 2014).

The most common metaphors used in reference to cancer involve variations of the WAR/INVASION concepts (Camus, 2012; Parikh,

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Kirch, & Brawley, 2015). Use of these bellicose terms in narratives directed at patients and at non-scientists has been sharply criticized since Susan Sontag's book *Illness as metaphor*, but also praised as a way to bolster the ability of patients and their caregivers to confront what are often painful and distressing treatment options (Harrington, 2012; Hauser, 2015; Kato, Cole, Bradlyn, & Pollock, 2008; Reisfield & Wilson, 2004; Stephenson & Witte, 1998). Biomedical investigators also often use variations of the WAR/INVASION metaphors inside the scientific community, particularly in reference to metastasis, one of the most salient characteristics of cancer. Study of the physical spread of cancer cells justifies use of a metaphor that is based on a geographic, and therefore spatial, concept. However, this metaphor does not account for the important role that intercellular communication plays in the current understanding of cancer biology, while also failing to include paraneoplastic syndromes and cachexia as part of the general understanding of cancer as a systemic disease.

3. Cancer cross-talk as molecular propaganda

Propaganda is information of a certain kind, information that most people associate with political indoctrination and/or advertising (Taylor, 2003). However, the common definition of propaganda extends to all messages that are "intended primarily to serve the interests of the messenger", messages that aim at "persuading people to do things which benefit those doing the persuading, either directly or indirectly" (Britannica, 2017; Taylor, 2003). Among the various scholarly definitions of propaganda, the one introduced by the philosopher Sheryl Tuttle-Ross states that propaganda is a message that is false, misleading, unwarranted or aimed at persuading an audience by being emotionally charged even if not necessarily false or misleading (Tuttle Ross, 2002, 2013). According to this definition, information becomes propaganda when such messages are used with the intention to persuade a socially significant group of people on behalf of an institution, organization or cause (Tuttle Ross, 2002, 2013).

The cross-talk bewteen cancer cells and their micro/macroenvironment is generally considered as biased, in that cancer cells are seen as broadcasting messages that mislead stromal cells, convincing them to act on behalf of the cancer. One could therefore say that cancer cells are excellent persuaders, that they spread information one may classify as propaganda both under the common and the scholarly definition of the term. Indeed, scientists' understanding of cancer biology is so imbued with the concepts of communication and of persuasion that the scientific literature on cancer research is replete with terms closely associated to propaganda: verbs like exploit, incite and orchestrate, adjectives like biased, misleading and exaggerated, and many more (Rotmistrov, 2006-2017). Furthermore, articulation of the role of the microenvironment in the development and spread of cancer often contains descriptions closely related to propaganda, as exemplified by statements indicating that cancer cells "conscript and corrupt resident and recruited normal cell types" (Hanahan & Coussens, 2012). Moreover, the commonly accepted 'seed and soil' theory of metastasis implies the propaganda-related concept of preparing the ground before effective action can take place, while the theory that cancer cells manage to survive by escaping recognition by the immune system involves concepts such as surveillance and censorship that are strongly linked to propaganda (Hart, 1982; Kuzet & Gaggioli, 2016; Taylor, 2003; Yeo, 2010).

Translating Tuttle-Ross's definition of propaganda into the molecular and cellular world of cancer, we can say that cancer cells produce messages that are used to persuade non-cancerous cells to act on behalf of the cancer. In translation, the false, misleading, unwarranted or charged messages become the molecules and microstructures cancer cells produce and release to persuade non-cancer cells to act on behalf of the growing neoplasm (it goes without saying that translation of the propaganda definition into the world of biology necessarily needs to strip any issue of intentionality and teleology form the relevant terms). Crucially, in defining protest songs as a form of propaganda, Tuttle-Ross stated that "there is no contradiction in having those singing also being the audience of the performance" (Tuttle Ross, 2013), i.e., those that generate and transmit propaganda can be part of the audience that responds and is influenced by those same messages. Going into metaphor, this concept would refer to the autocrine pathways cancer cells use to respond to the array of molecular messages they themselves produce, resulting in increased proliferation and other responses (Hanahan & Weinberg, 2011). Tuttle-Ross also stressed that in propaganda the "cause may change as events unfold" (Tuttle Ross, 2013), a concept we can apply to cancer by saying that the information broadcast by cancer cells changes continually as new needs arise during the growth, development and spread of cancer, from molecules that induce angiogenesis, to those that allow immune escape, to the set of messages that promote invasion and metastasis (this is not to suggest that these changes are linear and/or univocal).

Given the above, I propose to introduce the metaphor CANCER IS A PROPAGANDIST as a tool to render explicit the central role intercellular communication plays in scientists' current understanding of cancer. This metaphor is applicable irrespective of whether one chooses to use the common or the scholarly definition of the term propaganda.

Examples related to the hallmarks of cancer can help better clarify applicability of the metaphor (Hanahan & Weinberg, 2011). *Sustaining proliferative signaling* is considered the most fundamental trait of cancer. A central mechanism in the ability of cancer cells to proliferate without brakes involves these cells sending messages to stromal cells to persuade them to produce growth factors that promote proliferation of cancer cells. Another mechanism sees cancer cells' direct production of growth factors to which they respond in autocrine fashion, sometimes coupled with upregulation of growth factor receptors (cancer cells here would do both the singing and the listening in Tuttle-Ross's definition) (Hanahan & Weinberg, 2011). *Induction of angiogenesis* is another hallmark of cancer that can be directly linked to the concept of propaganda, with cancer cells producing factors that persuade a significant group of cells – endothelial cells, pericytes, macrophages, etc. – to promote generation of blood vessels that will then favor tumor development and growth. The enabling characteristic *Tumor-promoting inflammation* is but one additional example of effective persuasion via misleading or charged messages, with cancer cells producing cytokines and chemokines that act in both autocrine and paracrine fashion to exacerbate inflammation and immune infiltration that then promote cancer growth (Balkwill & Mantovani, 2012). I already mentioned the direct relation to propaganda of the 'seed and soil' theory, which is critical to the current understanding of the hallmark *Invasion and metastasis*. Here, "primary tumors can prepare the local microenvironment of distant organs for tumor cell colonization even before their arrival" (Liu & Cao, 2016), just as "before the battle, considerable planning to prepare the way is required" via propaganda (Taylor, 2003). Changing the meaning of information into a misleading or unwarranted message is another propaganda-related tactic used by cancer. An example that relates to the hallmark *Reprogramming energy metabolism* is the ability of cancer cells to rewire metabolic pathways to support cell growth and survival (Vander Heiden, 2011). Another relevant example is redirection of Transforming Growth Factor β signaling from suppression of cell proliferation to activation of the endothelial-mesenchymal transition process that promotes invasion and metastasis (Hanahan & Weinberg, 2011).