Abstract. The avalanche of research findings in complex multidisciplinary fields, such as cancer immunobiology, requests organizing and practical working models for scientists and clinicians. Frameworks from one scientific discipline can be adopted for another one, to clarify and provide new insights into complex findings. A ‘figure-ground’ (FG) perspective was adopted from cognitive sciences to construct a simple organizing tool, which can assist in understanding tumour development and immunotherapy designing. In an FG arena, there is a figure that needs to be contrasted from a background to be seen by a viewer, who may have a mental representation of the figure (i.e. knows what the figure features look like). Applying this framework to cancer, three players emerge: the viewer (immune system components), the figure (tumour), and the background (e.g., normal cells) with their dynamic interactions. Various characteristics of tumour development such as reduced expression of major-histocompatibility complex (MHC) molecules or infiltration by inflammatory cells in its boundaries make tumour-immunity interplay highly suitable to an FG perspective. We describe the basic FG framework and immuno-biology of tumour development, thereafter reframed by the FG framework. The term ‘antigenic contrast’ is introduced to reflect the contrast between the tumour figure and its variable background. Antigenic contrast emerges as a main factor enabling the immune system viewer to detect and mount adequate reactions against a tumour figure. We provide empirical examples of immunotherapeutic interventions whose results are explained by the FG perspective. For example, vaccines are forms of sharpening the ‘mental’ representation of the immune viewer concerning the tumour figure, while administering interferons can be seen as enhancing tumour figure salience by rescuing MHC expression. This framework highlights important elements in complex networks (e.g., cancer immunobiology), enhances communication between cancer scientists and clinicians, explains experimental and clinical study results, and provides further rationale for combinatorial immunotherapies.

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1. Introduction

Due to the avalanche of research findings in complex multidisciplinary fields such as cancer biology, scientists and clinicians need organizing and practical working models. This may be possible by adopting paradigms from other sciences. With this purpose in mind, we propose here the figure-ground framework adopted from cognitive-perceptual sciences to
review experimental findings and clinical research results in cancer-immunology.

2. Parallels between immunity and cognitive systems

Cohen suggested viewing the immune system as a cognitive system (1). Both systems are characterized by priming, memory and ‘mental representations’. In cognitive neuroscience, priming refers to a first exposure of the perceptual system to a stimulus, which facilitates later responses upon re-exposure to such a stimulus (2). The neural system creates assemblies of associated neuronal units, reflecting cognitive schemas of what general features of a concept/object look like: the mental representations. Memory activation is manifested by the associated neural units becoming active upon re-exposure to a previously presented triggering stimulus.

In immunity, priming involves a first efficacious contact between immune cells and an immunogenic antigen. This implies specific antigen recognition by pre-existing receptors expressed on adaptive immunity cells (T and B lymphocytes). Part of the activated cells will target the antigen, while another part will differentiate into memory cells, to establish a faster specific immune response during future re-exposures to the priming antigen. Finally, the panel of memory cells and antigen receptors can be considered as the immune system’s ‘mental representation’ of the antigenic environment it has been progressively exposed to (1). These parallels are crucial for viewing cancer-immunity networks in a cognitive-perceptual perspective, we now introduce.

3. The figure-ground framework

In cognitive-perceptual systems, a viewer is able to distinguish an object (figure) from its background. The degree of spatial impenetrability of elements in a picture, and the process of feedback between mentally represented boundaries (what things look like) and actually observed surfaces, help to distinguish a figure from the ground (3). Mapping this paradigm onto immunological contexts, the figure represents the immunological target (e.g., tumour cells) which the viewer (immunity) can detect and attack, depending on the figure’s contrast from its background (the context in which a tumour develops). The contrast may increase by enhancing the figure’s visibility, shadowing the background, or by sharpening the viewer’s mental representation of the figure.

4. A current view of tumour development and anti-tumour immunity

Current models of tumorigenesis shift from a cellular centred approach (cell transformation model) to focussing on tumour microenvironment and local inflammation (4-6). The tumour microenvironment includes the transformed cells and their products, the normal tissue cells, stroma, vessels, nerves, immune cells and all related products. When transformed cells become immortal and non-responsive to tissue homeostatic control (7), they begin to multiply, eliciting danger signals [e.g., heat-shock proteins, interleukin (IL)-1β, interferons -IFNs] (8). This activates a local acute inflammatory reaction, sustained by surrounding innate immunity cells (e.g., natural killer cells, macrophages) (9,10). Antigens from killed tumour cells are then processed by dendritic cells (DCs), and become bound to major histocompatibility complex (MHC) class I molecules. Together, they are presented to and prime cytotoxic T lymphocytes (CTLs). Activated CTLs specifically target the tumour, until eradication. This process also generates specific memory cells. However, several escape mechanisms (e.g., tumour down-regulated expression of MHC class I molecules (11); immunoeediting and immunoesculpturing (12), permit mutated cells to avoid immune surveillance and to multiply (13). This growth produces further stress on surrounding tissues. The newly elicited stress signals further sustain inflammatory responses, and the initially defensive, local and acute inflammation becomes chronic (14). Homeostatic anti-inflammatory and immunosuppressive mechanisms are stimulated (T helper type 2 - Th2; T regulatory cells - Tregs), and by suppressing CTLs, they paradoxically contribute to cancer progression (15).

5. Reframing tumour-immunity interplay by the figure-ground framework

To reframe the described and very complex dynamics of tumour development by the figure-ground (F-G) perspective, we need to identify three players: figure, background and viewer. At the beginning, the transformed cells represent a figure situated inside the background of a self-context - normal tissue (Fig. 1). The viewer is immunity and its components. It changes locations and functions during tumour development, as following.

Stage 1: Initially, when cells transform, their ‘non-self’ antigenic pattern may be insufficiently ‘strong’ to be distinguished by the immune viewer from the surrounding normal ‘self’ tissue (background). The viewer here is represented by nearby cells of innate immunity. Once danger signals are elicited by multiplication of transformed cells, the transformed cell figure achieves ‘perceptual’ (immunological) salience for the viewer. This triggers the viewer’s activation (immune cell migration and cell-mediated killing) (Fig. 1).

Stage 2: Tumour antigens are taken up and processed by antigen-presenting cells (APC: macrophages and DCs). DCs, migrating to lymph nodes, prime the second, more potent, viewer - CTLs. This activated second viewer (effector cells) specifically identifies the tumour figure for its eradication. This process enlarges and ‘sharpen’s the viewer’s mental representation of the tumour figure (Fig. 2). However, if the activated immune viewer fails to eradicate the tumour, transformed cells continue to replicate and elicit inflammatory signals, maintaining the tumour figure locally visible.

Stage 3: Expansion of the tumour and release of danger signals continues to stimulate recruitment of immune cells to surround, infiltrate, and join the tumour figure (Fig. 3A and B). The creation of the tumour microenvironment (including the tumour cells, the stroma and the previously activated local inflammatory network) produce changes in the original tumour figure, making the contrast between the tumour and its background weaker. Recruited immune cells include the first viewer (local innate-immunity cells) and the second viewer (CTLs). Progressively, the inflammatory network inside and near the tumour shadows the original tumour figure.
Stage 4: Persistence of inflammation triggers the response of a third viewer: systemic immunity (Fig. 3C). Its ‘attention’ is attracted to the inflammatory tumour microenvironment. Therefore, the chronic inflammatory network is seen as ‘THE’ homeostatic problem, instead of the tumour. Thus, systemic immunity mechanistically activates physiological anti-inflammatory regulatory responses (Th2, T-regs). This suppresses CTLs and other tumour-aggressing cells, and together with tumour-derived immunosuppressive molecules, contributes to tumour progression (14).

6. Antigenic contrasting of the tumour figure from the inflammatory background

Introducing the term ‘antigenic contrast’, we refer to the immunological salience obtained by the tumour cell antigenic phenotype (original figure and true target) relative to its background (inflammatory microenvironment or surrounding tissue). As described above, this contrast may decrease with tumour development. We hypothesize that adequate ‘antigenic contrast’ could rescue effective identification of the tumour figure in its obscuring background. Consequently, the F-G framework predicts that interventions aimed at increasing the antigenic contrast between the tumour figure and its inflammatory parts or its inflammatory background, should be done, for example, by: a) enhancing expression of tumour associated antigens (TAA) or inducing re-expression of MHC class I molecules on tumours (increasing tumour salience); b) ‘shadowing’ (suppressing) the inflammatory network; c) sharpening the viewer’s mental representation of the tumour figure using vaccines.

7. Empirical examples of immunotherapeutic figure-ground interventions

The role of the inflammatory background in an FG perspective can be easily seen when comparing germ-free (GF) with conventionally (CV) reared animals. In CV conditions, the commensal microbiota induces a highly regulated inflammatory network in the gut, known as ‘chronic physiological inflammation’ - CPI (16). Immune tolerance is induced, to avoid inflammatory damage of the mucosa. However, GF animals lack CPI and its elevated regulatory network (e.g., TGF-β, IL-4, IL-10). Following induction of colorectal
cancer, GF animals developed less and smaller tumours, and maintained higher anti-tumour immunological activity than CV animals (more cytotoxic cells, greater cytotoxicity, and more B cells). GF animals thus have a constitutively lower inflammatory background and are immunologically more ‘naive’ (they had more limited challenge by intestinal antigens, to be tolerated) than in CV conditions. These may have permitted greater salience of the tumour figure (adequate ‘antigenic contrast’), and reduced shadowing during progression in GF animals (17).

Use of anti-inflammatory drugs (e.g., COX-2 inhibitors, aspirin) to prevent colorectal cancer (18) can be interpreted as shadowing the inflammatory background. On the other hand, experimentally administering IFNs or histone deacetylase inhibitors (e.g., Trichostatin A) to rescue MHC class I expression (19,20), and tumour-cell engineering to increase immunogenic molecule expression on cell surfaces (21) may enhance figure salience. Vaccination, e.g. with TAA, DNA or DC vaccines, can sharpen the viewer’s ‘mental representation’ of tumour figures (tumour antigenic phenotype) (22).

Finally, the FG framework also provides a strong rationale for combinational treatments: sharpening mental representations by vaccines can be insufficient if the tumour figure is too weak or if it is shadowed. Experimental studies in vivo on animal models demonstrated that addition of anti-inflammatory (shadowing) medications enhanced the effectiveness of cancer vaccines (sharpened mental representation) (23). Similarly, administering a vaccine which included IFNγ (figure-enhancement by rescued expression of MHC-I), led to stronger anti-tumour responses than the regular vaccine alone (24). Finally, in humans with bladder cancer, aspirin (background shadowing) enhanced patients’ disease-free survival following vaccination with bacille Calmette-Guérin (25), a generic immune stimulator. Thus, as predicted by the FG perspective, sharpening the viewer’s representation of tumour antigens with vaccines and, either reducing the inflammatory background or enhancing the figure’s antigenicity, synergistically interact in favour of tumour eradication.

8. Conclusions and perspectives

The application of the FG framework from cognitive-perceptual sciences to the analysis of the tumour-immunity network showed its ability to serve as a tool for highlighting important aspects of a complex bio-medical process. The identification of the three main players inside the model of cancer microenvironment development, permitted to define and clarify the phases of their dynamic relationships and evolution. By doing this, the targets for therapeutic interventions were made more evident. We introduced the concept of ‘antigenic contrast’ as a major factor that permits the immune system (viewer) to effectively detect and target the tumour figure. Consequently, three possible modalities of intervention were identified to effectively increase the tumour figure salience and its eradication - by shadowing the inflammatory background, by sharpening the viewer’s representation of the tumour figure with a vaccine, or by re-establishing correct tumour antigenicity. Importantly, the FG framework also indicates the necessity and provides a rationale for combining these interventions to yield synergistically stronger and more effective anti-tumour responses. This framework appears to be a useful perspective tool to ‘catch the crux’ of biomedical problems (as tested here), for designing and guiding experimental and clinical approaches, and for enhancing communication between biologists and clinicians. These can all serve future translational research.

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