COMMENT

What are the hallmarks of cancer?

The seminal article by Douglas Hanahan and Robert Weinberg on the hallmarks of cancer is 10 years old this year and its contribution to how we see cancer has been substantial. But, in embracing this view, have we lost sight of what makes cancer cancer?

A major goal of cancer research is to understand how to counteract mechanisms that underlie the ability of cancers to kill the patient or, in other words, to be malignant. To this end, the puzzling complexity of numerous and interrelated properties of cancers was distilled 10 years ago into "six essential alterations in cell physiology that collectively dictate malignant growth: self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis" (Douglas Hanahan and Robert Weinberg)[1]. This guidance has been accepted with enthusiasm, as revealed by the phenomenal number of citations: 6,352 at the time of writing. Given such influence, it is only natural to use the tenth anniversary of this seminal article to ask a cautionary question: are the proposed hallmarks of cancer indeed such?

To answer this question, let us first agree on what is a hallmark. A hallmark is usually defined as 'a feature of something that distinguishes it from others'. As 'something' in our case is cancer the key question is what are the 'others' or, using laboratory jargon, what should we use as the negative control? To simplify our choice let us focus on solid cancers, which constitute the majority of diagnosed malignancy.

Because solid cancers are defined as malignant tumours and the cause of malignancy is our primary interest, arguably, the best negative control would be tumours that are not malignant, in other words benign tumours. The close relationship between benign and malignant tumours is shown by the fact that tumours of both types can be found in the same organs, can be derived from the same cell types, can reach the same size, can be induced by the same agents or hereditary mutations and can occur spontaneously[2–6]. The closeness of this relationship is further underscored by the fact that some benign tumours can become malignant, albeit rarely[2]. If we agree that benign tumours are the proper negative control for our thought experiment, then a hallmark of cancer should be a feature of malignant but not benign tumours.

Let us first consider that some benign tumours can weigh many kilograms at the time of diagnosis[7,8]. Because a mass of tissue larger than a few milligrams requires sustained angiogenesis to survive[9], we have to conclude that sustained angiogenesis is a feature of both benign and malignant tumours, a conclusion consistent with the available evidence[10,11]. It is also implausible that so many abnormal cells can accumulate and survive without evasion of cell death and insensitivity to antigrowth signals, as these are processes that control normal tissue homeostasis. Consistent with this argument, RB — a cell cycle control protein the deficiency of which was used to illustrate insensitivity to antigrowth signals[1] — is deficient both in retinoblastoma, a malignant tumour of the eye, and in retinoma, a benign tumour of this organ[6]. Likewise, evasion of apoptosis has been implicated in the pathogenesis of malignant and benign tumours[12–14]. Therefore, insensitivity to antigrowth signals and evasion of cell death also seem to be characteristic of both benign and malignant tumours.

The observation that the size of a tumour is not a definitive indicator of whether it is benign or malignant[3,4,15] seems to argue that the fourth hallmark — limitless replicative potential — is also shared by benign and malignant tumours, at least to the extent required to produce an equal number of tumour cells. Autocrine mechanisms have been implicated in the growth and maintenance of both tumour types[14,16–19], suggesting that the fifth hallmark, self-sufficiency in growth signalling, might also be common to both. The sixth hallmark, tissue invasion and metastasis, passes the test by definition: malignant solid tumours invade tissues and metastasize whereas benign tumours do not[2], some exceptions notwithstanding[20].

If five of the proposed hallmarks of cancer are also characteristic of benign tumours, why has it become so widely accepted to consider these features in the same league as tissue invasion and metastasis, which are responsible for most cancer mortalities? A tempting explanation is that the concept of the six hallmarks of cancer discussed by Hanahan and Weinberg[1] is more concise and lucid than the voluminous oncology textbooks and more likely to be read and used for guidance by basic scientists, such as myself.

However, another potential and more worrying explanation is that in many publications, including the article under discussion, the terms tumour and cancer are used interchangeably, perhaps because in the minds of many basic scientists these terms now mean the same thing.

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As a result, the idea that tumour development can result in a benign tumour that is unlikely to become malignant is often left out of the discussion. Consequently, a report that a genetic manipulation makes cells capable of producing tumours in laboratory animals is often automatically translated in our minds into a conclusion that this manipulation causes cancers, even when authors explicitly state that the tumours are not invasive or metastatic. A title such as 'Deficiency in gene X causes benign tumours' would alert the reader, but such a title would be an unlikely first choice for reporting the results.

Of course, as many examples have proved, studying the processes underlying the hallmarks of all tumours, benign and malignant, and the progression from one to the other helps us to understand the origin and development of cancers and in particular to learn how to diagnose and prevent them. However, keeping in mind the difference between tumours and cancers might also help us to focus more on mechanisms underlying the key emergent property of cancers, their malignancy. This change might help to correct the situation in which, after producing nearly two million papers on cancer, we are yet to understand when and how cancer cells metastasize[21,22] or to learn the underlying mechanisms sufficiently well to have a sizable impact on cancer mortality[23]. Otherwise, to use a military analogy, with the war on cancer about to enter its fifth decade, we might keep winning the battles, but losing the war.

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