Commentary

Cancer biomarker concentration changes during tumor progression

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Abstract

Introduction

Most circulating cancer and other disease biomarker concentrations increase during disease progression, roughly correlating with tumor burden or disease severity. During the biomarker discovery phase, several studies (some published in high-impact journals) report decreases in serum biomarkers at the time of disease diagnosis or during progression (in comparison to control, non-diseased populations). It is suggested these biomarker decreases between normal and diseased populations may have utility in diagnostics.

Methods

We briefly examine if a serum cancer biomarker concentration is likely to decrease as cancer progresses through empirical data.

Results

We propose a simple model, which, if correct, would suggest that in most cases, the biomarker decrease during disease progression could be an artifact or epiphenomenon (thus representing false discovery). Our suggestion is supported by the very few examples of decline of serum biomarkers during cancer development and progression.

Conclusions

The notion that a serum biomarker concentration could be inversely associated with tumor burden seems to be an epiphenomenon.

Introduction

Cancer biomarkers have important clinical applications, including screening, diagnosis, prognosis, and monitoring of patients' therapeutic response. Many contemporary discovery technologies, including genomics, proteomics, metabolomics, and other omics, revolutionized the way we identify and validate new biomarkers. New, and potentially clinically useful biomarkers are still published frequently in the literature. For example, a few candidate serum biomarkers for gliomas have just been published in the journal Science Advances by combining genomics and spatial multidimensional proteomics [1]. Despite the unequivocal progress and technological refinements in discovering new biomarkers, very few, if any, new serological markers have

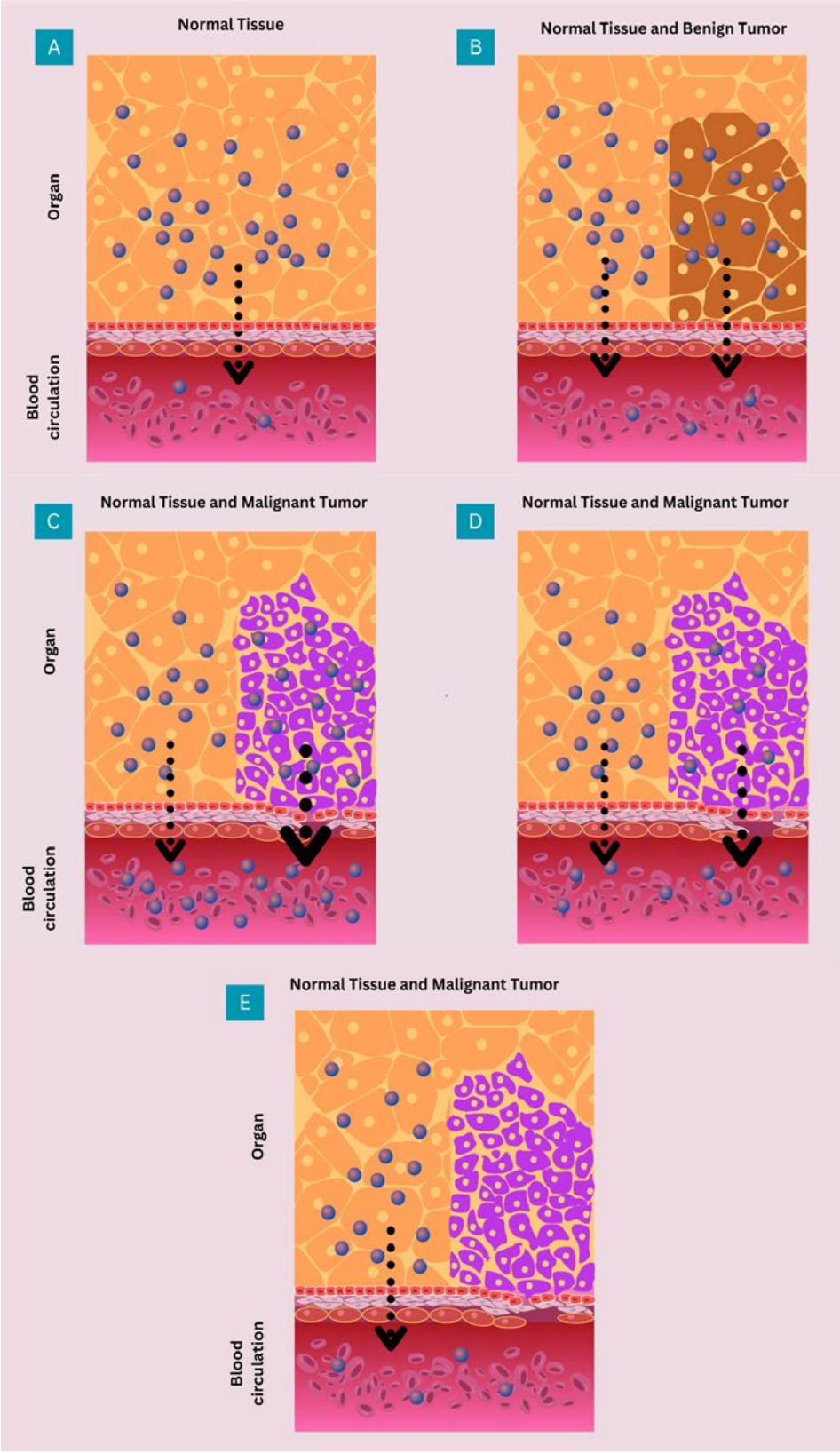
entered the clinic in the last 30-40 years. We and others have commented frequently on the failures of new cancer biomarkers to reach the clinic and identified numerous preanalytical, analytical and post-analytical shortcomings [2-4].

Among different classifications, cancer biomarkers can be grouped into two broad categories: those whose serum concentration is increasing in the presence and progression of malignancy (or as is alternatively stated "their concentration correlates with tumor burden") and those whose serum concentration presumably "decreases" with tumor presence or progression, in comparison to an appropriate non-diseased population. The first category of tumor markers is far more prevalent than the second one. We are not aware of clinically useful applications of circulating tumor markers which are inversely correlating with tumor burden. In this commentary, we speculate that many circulating tumor markers whose concentration is inversely related to tumor burden (i.e. their serum concentration decreases in comparison to controls when the tumor is first identified or is progressing) likely represent artifacts of the discovery process (false discovery) or epiphenomena. We further advocate that markers that decline with cancer progression should be carefully validated with well-defined groups of controls and patients, before definitive conclusions on their validity and clinical usefulness can be drawn.

The PSA paradigm

To illustrate our point, we will use the classical circulating prostate cancer biomarker, prostate specific antigen (PSA), as an example. In normal males, PSA is produced by the prostatic epithelial cells and is stored in the male reproductive system until ejaculation. The PSA concentration in seminal plasma is huge (~0.5 g/L) but only a minute fraction enters the systemic circulation, establishing a steady-state reference range of approximately 1 ug/L for adult males [5]. This is about a million times lower than the seminal plasma PSA concentration. Since normal prostatic epithelial cells and prostate cancer cells produce approximately the same amount of PSA on a cell-by-cell basis [5], the serum PSA concentration is not expected to be significantly altered when a patient develops prostate cancer. However, the sometimes-dramatic changes of serum PSA in prostate cancer patients (i.e. 100 ug/L or higher) are due to increased leakage of PSA from its vast normal reservoir (prostate tissue/seminal plasma) into the systemic circulation (Figure 1). There are numerous examples of tumor markers that increase in serum due to leakage from their respective, rich reservoirs (the contents of which normally, do not enter the circulation through physiological barriers). This mechanism of biomarker increase during disease state is similar to other commonly used non-cancer biomarkers, such as cardiac troponins; the latter increases dramatically in serum after myocardial infarction due to tissue damage/necrosis and the marker is released from its normal reservoir (cardiac muscle) into the circulation. Diagrammatic representations of a few scenarios are shown in Figure 1, which will be used for further discussion.

Figure 1: Diagrammatic representation of biomarker changes at various scenarios involving normal and cancerous tissues, as well as roughly equal biomarker expression or biomarker "downregulation".



The serum concentration of the biomarker will be dramatically increased only in Panel C. There is no circumstance in which the serum biomarker concentration will decrease below what is seen in non-diseased people. For more explanations see text.

Based on the information mentioned above, the increase of serum concentration of a biomarker at diagnosis (compared to controls) or disease progression, is easily explained (as shown in panel C). Biomarker leakage into the general circulation is the main reason for the observed increases during disease. As mentioned, biomarker decreases during cancer diagnosis (in comparison to controls) or progression, are rare in clinical practice and more difficult to explain. Most authors attribute such empirically observed serum biomarker decreases as biomarker "downregulation" in diseased tissues, which implies reduced transcription and/or translation of the biomarker in the disease (cancer) state in comparison to the normal state.

Panel A depicts a normal tissue (orange), acting as a reservoir of a (tumor) marker (blue dots), but the biomarker is not normally able to diffuse into the blood circulation due to the presence of physical barriers (epithelia, basement membrane, endothelia) and the tightly organized pattern of the prostatic cells. In such cases, the biomarker concentration differences between the reservoir (prostate; seminal plasma) and blood (red dots) can be as high as1,000,000-fold (as exemplified earlier by the PSA example).

Panel B depicts a benign tissue exhibiting biomarker expression per cell, roughly equal to that of the normal tissue. In this case, it is expected that the serum concentration of the biomarker will be modestly increased (2-3-fold) due to the larger amount of non-cancerous total tissue (normal tissue plus benign tissue). A good example of this is benign prostatic hyperplasia, whereby the size of the non-malignant prostatic tissue roughly increases by 2-3-fold. Panel C depicts a cancerous tissue exhibiting per cell, biomarker expression roughly equal to the adjacent normal tissue [5]. In this case, it is expected that the serum concentration of the biomarker will be dramatically increased due to leakage of the biomarker from the reservoir to the circulation due to the altered normal tissue architecture. In prostate cancer, the prostatic cells are disorganized and the layers between the prostate cells and blood vessels allow more PSA leakage into the circulation.

Panel D depicts a cancerous tissue exhibiting biomarker expression roughly equal to the normal tissue, but there is significant "downregulation" of the biomarker in the malignant tissue. In this case, the serum concentration of the biomarker is expected to increase, due to the additive effects of the biomarker originating from normal ad cancerous tissue. The biomarker increase will be higher if the biomarker is "upregulated" in the cancerous tissue.

Panel E depicts a cancerous tissue exhibiting total absence of biomarker expression. In this case the serum concentration of the biomarker is expected to be similar (but not lower) to the case of panel A, since the normal tissue will continue producing PSA while allowing a small fraction of PSA to diffuse into the circulation.

These examples illustrate that during cancer initiation and progression, the serum biomarker levels (assuming that the biomarker is produced by the tumor cells) are unlikely to decrease, even if in the cancerous tissue, the biomarker levels are generally "downregulated" or not expressed at all. One theoretical possibility is that the cancer cells may be inducing downregulation of proteins in normal tissue adjacent or distant to the cancer cells, during a process called "field cancerization" [6]. Otherwise, biomarker decreases in phase of cancer burden expansion should be viewed with caution and probably considered epiphenomena or false discovery. We are aware that there may be rare exceptions to our suggestion for certain tumors (pituitary carcinomas) where normal tissue destruction, coupled with the lack of biomarker production by the tumor, would lead to the decrease of the biomarker in the circulation [7].

Authors' Disclosure statements

MKC and EPD have no conflicts to report.

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