Minireview

Common ground in the transcriptional profiles of wounds and tumors

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Published: 26 May 2004

Genome ***Biology*** 2004, **5:**228

The electronic version of this article is the complete one and can be found online at http://genomebiology.com/2004/5/6/228

Abstract

Healing wounds and developing tumors are both sites of dynamic interactions between a variety of cell types. Recent microarray studies comparing wounds and tumors have identified characteristic similarities in gene expression that may prove to be useful for assessing cancer prognosis and for choosing subsequent treatment.

Tumors have long been described as sharing many histological features with repairing tissues, an idea that likens them to wounds that do not heal [1]. Such an analogy is tempting, as in both cases cell proliferation, survival and migration - in response to a cocktail of growth factors and cytokines - is accompanied by an inflammatory and angiogenic response [2]. Signals facilitating survival and invasion come from many sources in the tumor environment, with tumor cells, fibroblasts and endothelial cells producing various growth and differentiation factors, extracellular matrix proteins and proteases. These signals, together with other factors such as signaling mediated by cell-cell and cell-matrix interactions, activate a wide range of intracellular signaling cascades to affect cell motility and survival [3]. At a wound site, various cell types release the same growth factors and proteases, activating similar downstream signaling pathways [4].

Microarray analysis allows the screening of thousands of genes without a prior knowledge of, or bias for, which genes might be involved in the process being studied. It also allows the identification of panels of genes rather than individual ones, which may give a more complete picture of the process under investigation. Recent data have strengthened the link between tumors and wounds by providing molecular evidence of similar gene-expression profiles in keratinocytes at the wound margin and in squamous cell carcinoma [5]. Most recently, microarray studies using an *in vitro* model of the wound environment have identified a transcriptional signature for stromal fibroblasts, which may prove to be a useful clinical tool in assessing the stage of tumor progression [6].

Gene-expression profiling in a wound model

In pioneering work five years ago, the Brown lab used a DNA microarray approach to profile the genetic response of fibroblasts to serum, a fluid to which they should only be exposed in the context of a healing wound [7]. Accordingly, the spectrum of genes whose expression was upregulated included many whose products are implicated in key steps during wound repair - hemostasis, proliferation, migration, inflammation and angiogenesis - and many of these genes were subsequently identified in microarray-based searches for wounding-regulated genes [8,9]. In pursuing this line of research further, the Brown lab has recently used a broader approach to identify a canonical gene-expression signature of the response of fibroblasts to serum, and compared this with the publicly available mRNA expression profiles of a range of tumor and control tissue samples [6]. These genome-scale studies have again highlighted the similarities between wound repair and tumorigenesis, and suggest that the closer the match between a tumor's expression profile and a core set of genes induced by wounding, the worse the outcome for the cancer patient.

In a comprehensive study, Chang and co-workers [6] isolated fibroblasts from ten different anatomical sites and analyzed their transcriptional response following exposure to serum. Quantitating the expression of 36,000 human genes, they identified a common group of 677 genes that were either up- or downregulated by at least 1.5-fold in all populations. These were further pared down to a core of 512 genes whose expression was both serum-responsive and cell-cycle-independent;

this set of genes was defined as the fibroblast core serum response. Reasoning that the only place that fibroblasts are exposed to serum *in vivo* is where the tissue is undergoing repair or remodeling, the authors argue that the expression of core serum response genes in tumors may provide insight into the extent to which wound repair recapitulates tumorigenesis.

Epithelial migration and squamous cell carcinoma

Initial studies using laser capture microdissection to isolate cells, followed by microarrays to compare gene expression in oral squamous cell carcinoma and normal epithelium suggested that such a 'clean' approach might reveal changes in gene expression in malignancy [10]. In a further study from the same group, a similar approach was used to identify keratinocyte genes expressed in response to wounding; this study found that the transient changes that keratinocytes undergo during repair - hyperproliferation, migration and invasion - phenotypically resemble the response of keratinocytes during malignant transformation in squamous cell carcinoma [5]. Again using laser capture microdissection to isolate cells, mRNA was isolated from keratinocytes of the wound-edge hyperproliferative epithelium and from keratinocytes of unwounded epidermis. By hybridizing cDNA made from both populations to cDNA arrays, Pedersen *et al.* [5] identified 58 genes specifically expressed in the hyperproliferative epithelium during the repair process, of which more than a third were also expressed in squamous cell carcinoma. Where differences in gene expression were seen between wound healing and the carcinoma, they could be associated with the loss of growth control and the invasiveness that distinguishes malignant keratinocytes from wound-edge keratinocytes. Thus, in this study [5], it seems that while there are clear similarities between the gene-expression profiles of wound-margin keratinocytes and squamous cell carcinoma keratinocytes, the similarity decreases as the carcinoma keratinocytes become more malignant. This apparent difference may be because the keratinocytes covering a wound undergo transient changes to a migratory phenotype, whereas in squamous cell carcinomas the changes form part of a permanent and more aggressive progression.

Interestingly, comparison of the fibroblast signature with the expression profiles of various carcinomas (epithelial-derived tumors) revealed that the more the tumor signature resembles the fibroblast core serum response, the more likely the tumor cells are to metastasize, and thus the worse the prognosis is for the patient [6]. One explanation for this might be the occurrence of an epithelial-to-mesenchymal transition within the tumor. This would be likely to result in the upregulation of genes expressed more commonly in fibroblasts than in epithelia, and hence provide a link between the extent to which the epithelial-mesenchymal transition has occurred and the fibroblast core serum response. Thus it would be interesting to compare the results of Chang and co-workers [6] with expression-profiling data which described a set of genes specifically regulated during an epithelial-mesenchymal transition [11]. An intriguing possibility is that wound healing is accompanied by acute cell migration, invasion and proliferation caused by short-term signals, whereas long-term activation of the same signals might cause the irreversible progression towards epithelial-mesenchymal transition [12].

Predicting cancer progression

The concept that prolonged exposure to 'wound' signals at the tumor site causes cancer progression may be further supported by recent findings that challenge the dogma that metastases arise from a relatively small population of cells within a tumor that have a particularly high metastatic potential. Rather, microarray studies comparing metastatic and non-metastatic adenocarcinomas identified a molecular signature correlating with metastasis, and suggested that the bulk of cells within the tumor share this signature, and thus the metastatic potential is encoded within the bulk of the primary tumor [13]. This signature, defined as 17 differentially regulated genes, correlated with metastatic potential in solid tumors from a variety of organs, supporting the concept of a common pathway towards metastasis, and suggesting the existence of common therapeutic targets in different cancers.

Gene-expression profiling has also been reported to be useful for predicting the clinical outcome of breast cancer [14]. DNA microarray analysis of primary breast tumors from 117 patients revealed a 'poor prognosis' gene-expression signature, consisting of genes regulating the cell cycle, invasion, metastasis and angiogenesis. Signatures such as these can then be used in patient screening to select those patients who would benefit from receiving chemotherapy or hormonal therapy that reduces the risk of distant metastases three-fold but provides no benefit for the majority of patients receiving it. Thus many patients could be spared the harmful side effects of a non-beneficial therapy.

Understanding repair and identifying targets

Harnessing the power of microarray technology to provide reliable insight into clinically significant problems, including wound repair and tumorigenesis, presents a potentially attractive aid in deciding on the appropriate treatment. Thus far the use of microarrays in predicting cancer outcomes has shown variable prognostic performance, however, and one slight concern is that a publication bias towards positive studies may exaggerate the power of gene-expression profiling [15]. Key to the future application of microarrays as a prognostic tool will be the rigorous design of larger studies with complete cross-validation of results, such as that shown when comparing the core serum response with tumor signatures from independent studies of a variety of adenocarcinomas [6,13,14].

As microarray technology becomes more widely available, we can hope to see a vast growth in the understanding of the signaling events that control the wound-repair process. Given the similarities between wound repair and tumorigenesis, novel findings in the wound-repair field may help to identify new targets for cancer therapy. Tantalizingly, small-molecule drugs, such as non-steroidal anti-inflammatory agents and imatinib mesylate, which target cyclooxygenase-2 [16] and platelet-derived growth factor, respectively [17], are efficacious in treating or preventing cancer. Since both cyclooxygenase-2 and platelet-derived growth factor are key proteins in the response of fibroblasts to serum, it is tempting to speculate that as we learn more of the global genetic response to wounding, we may identify valuable targets for therapeutic intervention.

Acknowledgements

I am extremely grateful to Sabine Werner and Clive Dickson for critical reading of this manuscript and to Cancer Research UK for funding.

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