"Tumors are wounds that do not heal" is a well-known statement of the Harvard Medical School pathologist Prof. Harold Dvorak. He recognised that the tumor microenvironment (stroma and the associated extracellular matrix) strongly resembles the granulation tissue generated in skin wounds. Therefore, it seems likely that malignant tumors induce their stroma by activating the wound healing response of the host. In contrast to wounds, however, the process is not self-limiting, resulting in uncontrolled cell proliferation, invasive growth and eventually metastasis. In the past few years Dvorak’s hypothesis was strongly supported by experimental studies, and various parallels between wounds and tumors were identified at the cellular and molecular level. Interestingly, it has been shown that many genes that are up-or downregulated upon skin injury are similarly regulated in malignant tumors. Therefore, it is of particular interest to identify and functionally characterise wound-regulated genes and to determine their roles and mechanisms of action in cancer.

One of the genes that are strongly upregulated upon injury to various tissues and organs encodes the growth and differentiation factor activin. Although activin expression/function has been studied in several types of cancer, its role in keratinocytic skin cancer has previously not been addressed. The two major types of keratinocytic skin cancer are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Currently, between 2 and 3 million non-melanoma skin cancers occur globally each year. One in every three cancers diagnosed worldwide is a skin cancer, and the life time risk of developing skin cancer is 1: 5 in the US. In recent years, their incidence continuously increased, in particular due to prolonged sun exposure, use of tanning beds and also the increased life expectancy. Furthermore, immunosuppressive therapy after organ transplantation strongly increases the risk of developing cutaneous squamous cell carcinomas, and the tumors are particularly aggressive in these patients. Although epithelial skin cancers rarely metastasize, they grow invasively and their removal often leads to severe functional and aesthetic impairments. Therefore, there is a strong need for the development of cost effective and well tolerated therapies. This requires a thorough understanding of the mechanisms underlying the pathogenesis of skin cancer.

In the current project that was funded by the European Commissions FP7-PEOPLE-IEF-2008, we could demonstrate an important role of activin in the development and progression of keratinocytic skin cancer. Using two different mouse models of non-melanoma skin carcinogenesis (chemically-and virus-induced), we found a strongly enhanced tumor incidence and multiplicity as well as accelerated malignant progression of the tumors in transgenic mice overexpressing activin in keratinocytes compared to the control animals. We could show that this pro-tumorigenic effect of activin is not mediated via keratinocytes, but through induction of a pro-tumorigenic microenvironment (recruitment of immune cells). This included accumulation of a tumor-promoting subpopulation of T cells (aß T cells) in the skin through activin-induced expression of certain chemokines. In parallel, there was a loss of the tumor-suppressive epidermal T cell subpopulation (?d T cells) during tumor promotion, since activin strongly suppressed their proliferation that occurs in hyperproliferative skin. These findings are likely to be important for human skin cancer, since we found strongly enhanced levels of activin in biopsies from patients with basal and squamous cell carcinomas. The malignant keratinocytes themselves as well as endothelial cells in the tumor stroma were identified as the major source of activin in the tumor. Moreover, T cell infiltrates (and in particular a subpopulation of aß T
cells, regulatory T cells) that we found to accumulate in our mouse models in the presence of high activin levels, have been shown to associate with human SCCs and to be responsible for the generation of a tumor promotive microenvironment. These findings further strengthen the relevance of our data for the human situation.

In conclusion, we identified a novel pro-tumorigenic protein involved in the development of non-melanoma skin cancer, and thus defined a new potential target for prevention, alleviation and/or cure of these cutaneous malignancies. If successful, targeting activin may result in an improved quality of life for the patients concerned. Importantly, activin antagonists were recently shown to reverse cancer cachexia and muscle wasting as well as cancer-induced bone destruction in animal models, and they are in clinical trials for the treatment of these severe symptoms in cancer patients. Thus, it may well be that targeting activin action by activin antagonists could inhibit growth and progression of certain types of tumors and at the same time prevent cancer-induced morbidity. Experiments to test this hypothesis in animal models are currently underway. Therefore, data gained from this EC founded project are not only of high scientific importance, but may also be directly translated into a new therapeutic approach.

**Reported by**

EIDGENÖSSISCHE TECHNISCHE HOCHSCHULE ZÜRICH
18, Schafmattstrasse
8093 ZURICH
Switzerland

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