

Regulation of skin tumorigenesis by integrin $\alpha 3\beta 1$

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Ethical review	Approved WMO
Status	Pending
Health condition type	Skin neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON44700

Source

ToetsingOnline

Brief title

Integrin $\alpha 3\beta 1$ in skin carcinogenesis

Condition

- Skin neoplasms malignant and unspecified

Synonym

immunohistology, Integrin $\alpha 3\beta 1$

Research involving

Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis

Source(s) of monetary or material Support: KWF

Intervention

Keyword: cell adhesion, histology, integrin, skin carcinogenesis

Outcome measures

Primary outcome

none

Secondary outcome

none

Study description

Background summary

Integrins are $\alpha\beta$ heterodimeric adhesion receptors that play an important role in maintaining epithelial integrity. In the skin, the major integrins $\alpha2\beta1$, $\alpha3\beta1$ and $\alpha6\beta4$ connect the cytoskeleton of basal keratinocytes to the underlying basement membrane. Besides their key function in skin physiology, these integrins also have been implicated in the development and progression of SCCs. Mouse models in which different integrins are either overexpressed in the suprabasal epidermis or mutated in the whole animal showed altered susceptibilities to chemically induced skin tumorigenesis. Increased expression of $\alpha2\beta1$, $\alpha3\beta1$ and $\alpha6\beta4$ has been observed in hyperproliferating human cancers of the head and neck. Integrins thus seem to play a role in the initiation and promotion of tumors.

The integrin $\alpha3\beta1$ is one of two receptors (the other being $\alpha6\beta4$) expressed by basal keratinocytes that bind to laminin-332 and -511 in the epidermal basement membrane. It forms a stable complex with the tetraspanin CD151, which strengthens the adhesion mediated by $\alpha3\beta1$. Recently, we showed using epidermis-specific knockout mice for the genes encoding the $\alpha3$ subunit (*Itga3*) or CD151 (*Cd151*) that both genes are required for the efficient formation of skin tumors following exposure to carcinogen (1,2). In the absence of $\alpha3\beta1$, epidermal turnover is increased leading to depletion of slow-cycling keratinocytes, which are thought to be the cells-of-origin of epidermal cancer. Loss of $\alpha3\beta1$ in benign tumors reduces proliferation, but increases tumor progression in advanced SCCs. Similar effects are observed in epidermis-specific *Cd151*-knockout mice. Epidermal turnover is associated with loss of slow-cycling keratinocytes. As a result, fewer tumors are formed after exposure to carcinogen. In contrast to the consequences of the loss of $\alpha3\beta1$, these effects are dependent on the presence of TPA that increases proliferation

and migration, but decreases adhesion.

Study objective

The primary objective is to evaluate possible clinical effects correlated with $\alpha 3\beta 1$ and CD151 expression in human epidermal malignancies, and relate these findings to the effects of $\alpha 3\beta 1$ and CD151 deficiencies in skin cancer in the mouse. Specifically, we will determine whether in benign hyperplastic lesions of the skin (actinic keratosis, keratoacanthoma) the expression of $\alpha 3\beta 1$ and CD151 is increased, but decreased if they are malignant transformed into squamous cell carcinomas (SCCs) in situ (Bowen disease) and subsequent progression to invasive SCCs and spindle/anaplastic SCCs. Unfortunately, none of the commercially available antibodies against human $\alpha 3$ and CD151, reliably react with formalin-fixed paraffin-embedded (FFPE) tissues. Therefore we wish to examine the expression of these antigens as well as those of associated proteins (e.g. FAK, ILK, etc) on freshly frozen normal, pre-malignant and tumor material. It is anticipated that for these (pilot) experiments we will need eight skin biopsies for each type of lesion from different patients. Establishing a correlation between the expression of $\alpha 3\beta 1$ and the histological grade in human skin cancer may provide important prognostic and therapeutic information.

Study design

This is an observational study, investigating the expression pattern of integrins and associated proteins on frozen sections of normal skin, keratosis actinica, etc. It concerns a pilot experiment exploring the possibility whether there is a correlation between the level of expression of these proteins and the grade of tumor. The experiment involves groups of 8 patients each with a distinct type of tumor. As a control we will compare the level of expression of the various proteins in the different types of tumors with that in normal skin obtained from the same patient. If the results of these preliminary experiments are promising we will expand the study by including more patients to render the data statistically significant.

Study burden and risks

The burden and risks associated with participation in this study are negligible

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Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

- Be 18 years or older.
- Histologically confirmed keratoacanthoma, actinic keratosis, Bowens disease or squamous cell carcinoma.
- Lesions have to be either in the head and neck region or on the trunk and extremities.

Exclusion criteria

- If receiving any anti-cancer therapies
- Prior surgery, radiotherapy or cryotherapy in the affected skin area.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL	
Recruitment status:	Pending
Start date (anticipated):	01-10-2013
Enrollment:	0
Type:	Anticipated

Ethics review

Approved WMO	
Date:	07-11-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	12-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL45955.031.13