Regulation of skin tumorigenesis by integrin α3β1

Published: 07-11-2013
Last updated: 23-04-2024

The primary objective is to evaluate possible clinical effects correlated with α3β1 and CD151 expression in human epidermal malignancies, and relate these findings to the effects of α3β1 and CD151 deficiencies in skin cancer in the...

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 α3β1 in skin carcinogenesis

Condition

- Skin neoplasms malignant and unspecified

Synonym
immunohistology, Integrin &alfa;3β1

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 αβ heterodimeric adhesion receptors that play an important role in maintaining epithelial integrity. In the skin, the major integrins α2β1, α3β1 and α6β4 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 α2β1, α3β1 and α6β4 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 α3β1 is one of two receptors (the other being α6β4) 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 α3β1. Recently, we showed using epidermis-specific knockout mice for the genes encoding the α3 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 α3β1, 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 α3β1 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 α3β1, 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 α3β1 and CD151 expression in human epidermal malignancies, and relate these findings to the effects of α3β1 and CD151 deficiencies in skin cancer in the mouse. Specifically, we will determine whether in benign hyperplasic lesions of the skin (actinic keratosis, keratoacanthoma) the expression of α3β1 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 α3 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 α3β1 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
.

Contacts

Public
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL
Scientific
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL

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