RUDN Journal of Agronomy and Animal Industries. ISSN 2312-797X (Print). ISSN 2312-7988 (Online)
Вестник РУДН. Серия: АГРОНОМИЯ И ЖИВОТНОВОДСТВО
2024;19 (1): 165—175
http://agrojournal.rudn.ru

Veterinary science
Ветеринария

DOI: 10.22363/2312-797X-2024-19-1-165-175
EDN: AYIMKC
UDC 616

Research article / Научная статья

The role of Wnt and Shh signaling systems in noggin-induced tumorigenesis

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Abstract. The cross-interaction between BMP, Wnt and Shh signalling pathways in developing epithelial skin tumours remains poorly understood. To study the role of Wnt and Shh signalling pathways in tumour development upon BMP inhibition, we utilized a transgenic mouse model, overexpressing BMP antagonist noggin in the skin epithelium and leading to the development of hair follicle-derived tumours shortly after birth. Comparative gene and protein expression analyses revealed up-regulation of Wnt and Shh signalling systems in the skin of transgenic mice at various stages of follicular tumour development. Furthermore, recombinant BMP-4 suppresses the expression of Shh in the culture of tumor cells, while pharmacological inhibitors of Wnt and Shh significantly slow down the formation and development of tumors in noggin-expressing transgenic mice. These results enhance our knowledge about the role of growth factors in carcinogenesis and may lead to finding new targets for specific therapies for oncological diseases.

Keywords: signaling pathways of BMP, noggin, tumors, skin, transgenic mice

Conflict of interests. The authors declare that they have no conflict of interests.

Article history: Received: 20 July 2022. Accepted: 13 November 2023.

For citation: Mardaryev AN, Mardaryev NS, Mardaryeva NV, Shchiptsova NV. The role of Wnt and Shh signaling systems in noggin induced tumorigenesis. *RUDN Journal of Agronomy and Animal Industries*. 2024;19(1):165–175. doi: 10.22363/2312-797X-2024-19-1-165-175

Introduction

Recent studies have increasingly pointed to the role of disorders in the intracellular transmission of the BMP signal in the development of tumorsin different organs, including the skin. The most convincing data on the importance of bone morphogenetic proteins (BMP) in carcinogenesis were obtained in the genetic study of syndromes with familial forms of cancer [1]. Germinative mutations of BMPR-IA (Alk3) have also been found in Cowden syndrome [2]. Moreover, aberrations in the BMP signaling pathway were also found in the study of most (more than 85 %) sporadic cancer processes in humans. However, the role of BMR in carcinogenesis is quite complex, both pro- and anti-tumor effects have been described [3, 4]. Despite the enormous progress made in determining the functional significance of BMP in carcinogenesis over the past decade, little is known about the molecular mechanisms involving the BMP signaling pathway in skin carcinogenesis.

Wnt and Shh signaling pathways are necessary for normal development and postnatal remodeling of the skin [5]. However, their aberrant activation leads to several epithelial tumors, including squamous cell carcinoma and basal cell carcinoma of the skin [6–11]. Thus, it can be assumed that the cross-interaction between BMP, Wnt and Shh signaling pathways in developing epithelial skin tumors.

The aim of the study is to investigate the impact of the BMP antagonist Noggin on BMP's anti-tumor activity in skin tumour development. This will be achieved by using a transgenic mouse model that overexpresses Noggin in keratinocytes. The study will focus on observing dynamic changes in skin tumor development, performing a comparative analysis of the expressions of key components of Wnt and Shh signaling systems in the transgenic mice at various stages of skin tumor development. We will also look at the expression of the stem cell markers in the developing tumors. As noted in our previous works, the activity of stem cells necessary for maintaining the cellular identity and differentiation into specialized cell types is controlled by BMP and polycomb (PcG) proteins, which perform the function of transcriptional repressors [12–16].

Materials and methods

1. *Animal experiments* were conducted according to protocols approved by the University of Bradford (license PPL 40/2989). The mice were in shared cages with a 12-hour light period and free water and food access. A transgenic mouse line (TG) overexpressing noggin, a BMP antagonist, was produced by cloning mouse noggin cDNA into a genetic construct under the control of Keratin promoter 14 (K14) [17].

FVB mice from Charles River Company were used as controls (WT). To study the role of noggin overexpression in the early stages of follicular tumor development, back skin samples were taken from TG and WT mice at the following time points: 0, 4, 10, 14, 20, 24, 28, 32, 36, 40 days of postnatal ontogenesis (P0 — P40, respectively), as well as at 12 and 24 weeks. Five-seven TG and age-matched WT control mice were selected for each indicated time point. Skin samples were immediately frozen in liquid nitrogen and embedded in Tissue-Tek, O.S.T. 4583 Compound (Sakura, USA) with subsequent storage at –80 °C.

To induce skin tumors, a two-stage chemical carcinogenesis protocol was employed using a carcinogen 7,12-dimethylbenz[a]antracen (DMBA) (Sigma-Aldrih) and a tumor promoter 12-tetradecanoil-phorbol-13-acetate (TPA) (Sigma-Aldrih). The back skin of 8-week-old female TG and WT mice (n = 5 for each mouse strain) was shaved and treated with a single dose of DMBA (250 μg/ml) followed by a twice-per week application of TPA (40 μg/ml) for 15 weeks. Tumor progression was observed up to 25 weeks. The size and number of tumors were measured.

Wnt antagonist Aptosyn (4 mg/kg; OSI Pharmaceuticals, USA) and Shh inhibitor Cyclopamine (100 μg/kg; Tocris, USA) were used to study the role of Wnt and Shh signaling pathways in trichofolliculoma development. TG mice (n = 24) received daily subcutaneous injections of Aptosin or Cyclopaminein the dorsal area from day P10 to P28 of the postnatal life. The skin was collected for histological and morphometric analyses. Based on the morphology, HF-derived tumors were divided into several groups: stage 1– small tumors (< 60 μm in diameter) arising from the HF outer root sheath, stage 2 — medium-sized tumors (60…120 μm in diameter), stage 3 — single large tumors (>120 μm in diameter), stage 4 — multiple large tumors with epithelioid cyst containing keratinized substance in the center. The percentage of the HFs with tumors at the distinct stages of development was assessed in the Aptosyn (P19) and Cyclopamine-treated (P21 and P28) groups versus vehicle control. These data were combined and statistically analyzed using an unpaired Student's t-test using GraphPad Prism 6 statistical software.

2. *Isolation and culture of K14-noggin trichofolliculoma cells.* Large visible tumors were dissected from the skin of five 4–6 month-old TG mice and minced with scissors in the growth medium (William's E medium supplemented with 10 % FBS), followed by treatment with Collagenase/Dispase (Roche, 1mg/ml) for 1 h at +37°C. Single-cell suspension of tumor cells was prepared by filtering the minced tumor tissue through a 70-μm nylon mesh (Becton Dickinson), followed by centrifugation for 3 min at 100× g, and resuspension with fresh growth medium. Cells were seeded onto collagen-coated P60 plates and cultured at +33 °C with 8 % CO_2 until 80…90 % confluency. The tumor cells were treated with either 200 ng/ml BMP4 alone, 200 ng/ml BMP4 and 500 ng/ml Noggin (R&D Systems), or vehicle control for 24 hours. Cells were processed for total RNA and protein isolation.

3. *RNA isolatiuon and Quantitative RT-PCR.* Total RNA was isolated with TRIZOL reagent (Invitrogen) according to the manufacturer's protocol. For cDNA synthesis, 1μg of the total RNA was used with SuperScript III First-Strand Synthesis System (Invitrogen), and 0.5 μl of the synthesized cDNA was used for gene expression analysis

in the reaction mixture containing 1x iQ SYBR Green Supermix (Bio-Rad) and 0.5 uM forward and reverse primers. qRT-PCR was performed using MyiQ Single-Color Real-Time PCR Detection System (Bio-Rad). PCR primers were designed with Beacon Designer software (Premier Biosoft International; Table 1). For each gene of interest, ΔΔCt method was employed to calculate relative gene expression using *Gapdh* as a reference gene. qRT-PCR was performed in triplicates, and data were pooled and presented as mean ± SEM. Statistical analysis was performed using unpaired Student's t-test using GraphPad Prism 6 statistical software.

Table 1

List of PCR primers

Accession Number	Sequence Definition	Sense/Anti-sense Primers
NM_009170	Sonic hedgehog (Shh)	CATTCCTCTCCTGCTATGCTCCTG ATGACAAAGTGGCGGTTACAAAGC
NM_011915	Wnt inhibitory factor 1 (Wif1)	CCACCTGAATCCAATTACATC TGAACAGCATTTGAACATCC

4. Immunofluorescent analysis was performed on skin cryosections (9 μm) fixed in acetone (10 mins at –20 °C) or 4 % PFA (10 mins at room temperature). Sections were incubated with primary AB (Table 2) at +4 °C overnight, followed by corresponding FITC- and TRITC-labeled secondary AB (Jackson ImmunoResearch) for 1hr at +37 °C. Cell nuclei were visualized with 4'6'-Diamidino-2-phenylindol (DAPI). Images were acquired using Nikon Eclipse epi-fluorescent microscope in combination with SPOT digital camera and image analysis software (Diagnostic Instruments).

Table 2

List of primary antibodies

Anigen	Host	Dilution	Manufacturer
β-Catenin	Mouse	1:100	Sigma
Lef1	Rabbit	1:100	R&D Systems Inc
Lhx2	Goat	1:250	Santa-Cruz Biotechnology
Sox9	Rabbit	1:200	Santa-Cruz Biotechnology
Wif1	Goat	1:1000 (Tyramideamplification)	R&D Systems Inc.
Wnt10b	Goat	1:100	R&D Systems Inc.

5. RNA in situ hybridization was performed on tissue cryosections (9 μm) as previously described [18]. DIG-labeled RNA probes for the detection *Ccnd1* and *Ccnd2* were kindly provided by Prof. A. Dlugosz (Department of Dermatology and Comprehensive Cancer Center, University of Michigan, USA).

Results and Discussion

Overexpression of BMP antagonist noggin in mouse skin leads to tumors arising from hair follicle outer root sheath, which resemble human trichofolliculoma morphologically (fig. 1, A, B). To test whether BMP inhibition in the epidermis affects the development of chemically-induced skin tumors, WT and TG mice were treated with a chemical carcinogen DMBA. In TG mice, the first papillomas emerged as early as six weeks after DMBA treatment (fig. 1, D), while WT mice developed the skin tumours much later, by 11 weeks of the treatment (fig. 1, C). Moreover, TG mice showed an over 5-fold increase in the total number of skin tumours in TG compared to WT mice by the end of the experiment (fig. 1, D, C). These data demonstrate that BMP inhibition increases susceptibility to skin carcinogenesis.

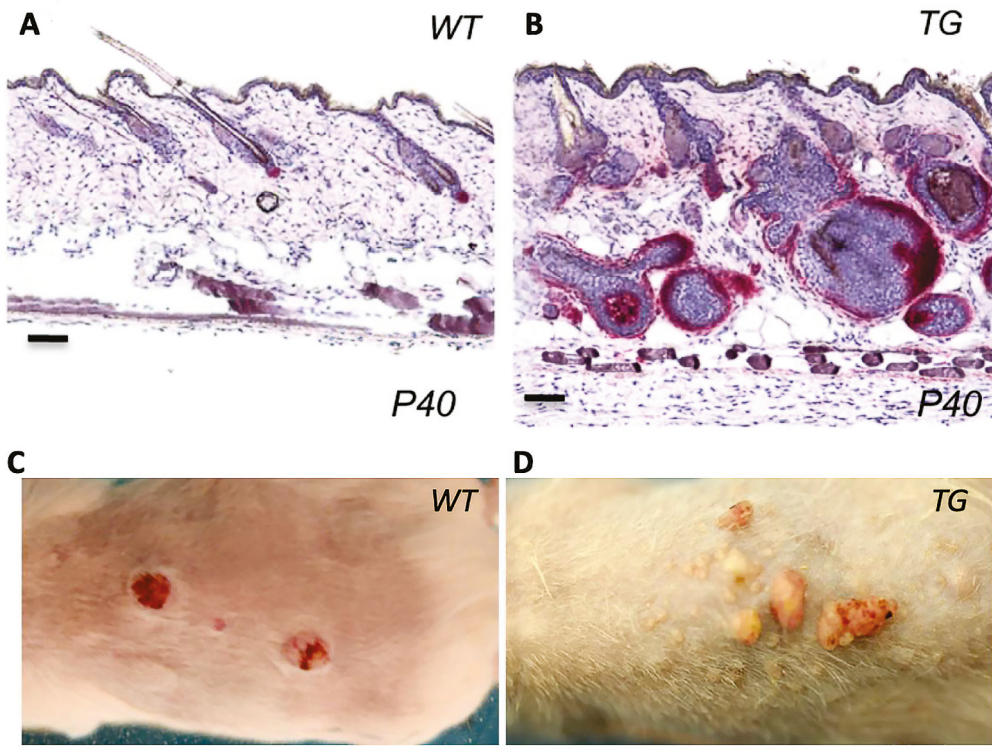

Fig. 1. Developing hair follicle-derived tumors in transgenic mice overexpressing BMP antagonist noggin in the skin: A, B — Hematoxylin/Alkaline Phosphatase staining of skin sections from TG and WT mice at P40, scale bar — 200 um; C, D — macroscopic images of the back skin showing chemically-induced skin tumors in WTand TG mice following 20 weeks of DMBA/TPA treatment

Source: made by authors

We performed immunofluorescent and quantitative RT-PCR analyses to probe into molecular mechanisms of the trichofolliculoma development in K14-noggin mice. The immunofluorescence analysis revealed an increased Wnt10b, Lef1, and β-catenin protein expression at the early stages of follicular tumor development (tumor placodes) in TG mice, whereas their expression is markedly reduced in the developed tumors (fig. 2, A–C).

These data indicate that activation of the Wnt signaling pathway is associated with tumor initiation upon BMP imhibition. Interestingly, the immunofluorescent analysis revealed that most tumor placode cells also express stem cell markers such as Lhx2, and Sox9 (fig. 2, C, D). This finding may suggest that the hair follicle stem cells in the bulge region initiate tumor growth upon noggin overexpression. It is known that under normal conditions, activation of the Wnt signaling pathway occurs in the early phase of anagen when the hair follicle stem cells actively divide to fuel new hair growth [19]. It can be assumed that the mechanism of initiation of K14-Noggin tumors has much in common with the regeneration of the hair follicle during the hair cycle and includes activation of the Wnt signaling system. On the other hand, the expression of the Wif1, a Wnt antagonist, was not observed in tumor placodes. On the contrary, Wif1 was actively expressed in the bulge stem cell area in control mice (fig. 2, E). These data indicate the involvement of Wif1 in regulating the activity of normal stem cells and/or early progenitor cells in hair follicles. The decrease in Wif1 expression in the skin of TG mice and increased expression upon BMP4 treatment (fig. 2, F) further suggest that Wif1 is a BMP target, serving as an intermediary between BMP and Wnt signaling pathways in the skin.

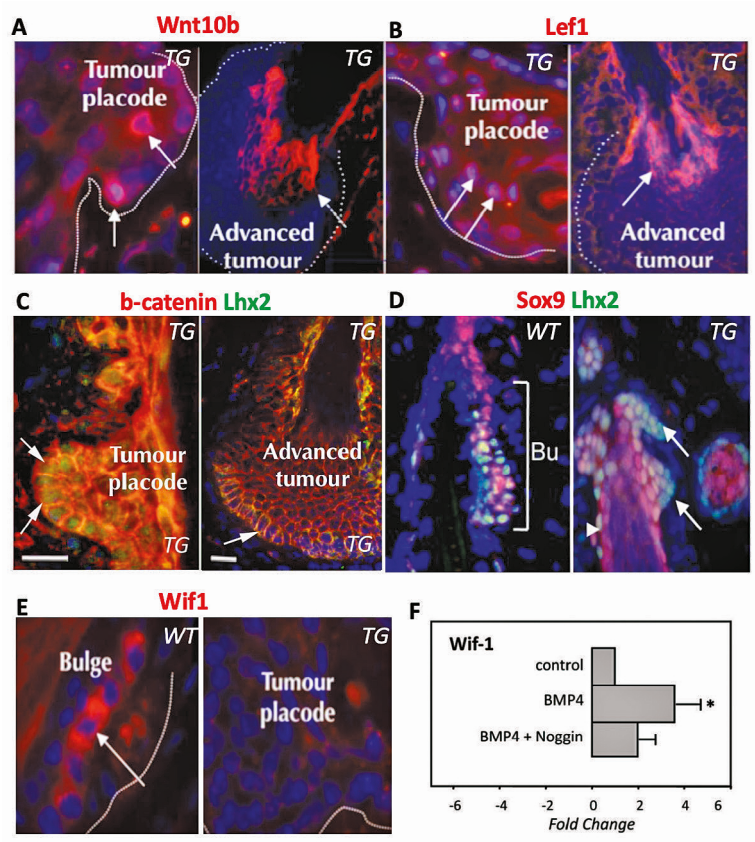

Fig. 2. Analysis of Wnt pathway components expression and stem cell markers in tumor placodes and more advanced tumors

Source: made by authors

Treatment of the K14-noggin tumor cells with BMP4 resulted in a significant decrease in *Shh* transcript expression, suggesting an antagonistic interplay between BMP and Shh pathways (fig. 3, A). For a more detailed study of the role of the Shh signaling pathway in the hair follicle tumor development in TG mice, we analysed the expression of its target genes by in situ hybridization. Transcripts for Cyclin D1 (*Ccnd1*) and Cyclin D2 (*Ccnd2*), which are known target genes of Wnt and Shh signaling pathways [20], were detected in tumor placodes, but their expression level was significantly enhanced in more developed tumors (fig. 3, B, C). Thus, these results strongly suggest that the formation of tumors in K14-Noggin mice was accompanied by activation of the Shh signaling pathway.

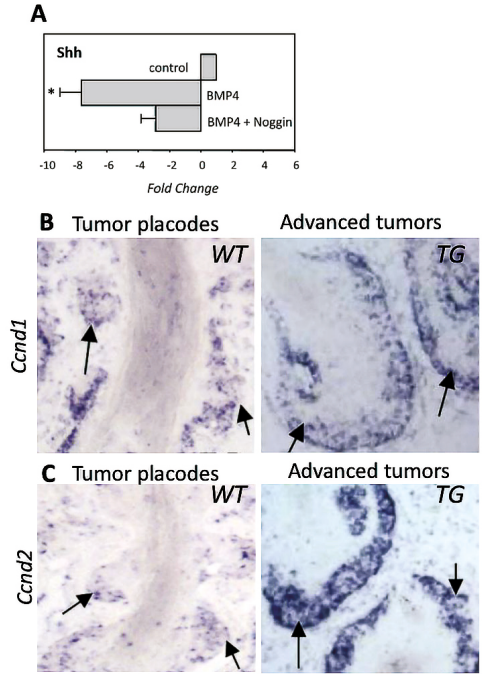

Fig. 3. Expression of *Shh* and its target genes *Ccnd1* and *Ccnd2* in noggin-overexpressing tumor cells
Source: made by authors

To elucidate the functional role of Wnt and Shh sinaling pathways in the development of tumors in K14-Noggin mice, we performed a pharmacological experiment using Wnt and Shh antagonists aptisin and cyclopamine, respectively [21, 22]. Inhibition of Wnt signaling by aptisisn resulted in a significant reduction of tumor-bearing hair follicles ($p < 0.05$) (fig. 4, A). In contrast, cyclopamine had no effect on the total number of hair follicles with developing tumors; however, there was a marked decrease in the advanced-stage tumors (stage III) (fig. 4, B). This study showed that Wnt signaling is required for tumor initiation, while the Shh pathway promotes and sustains tumor growth, possibly via increased Cyclin D1 and D2.

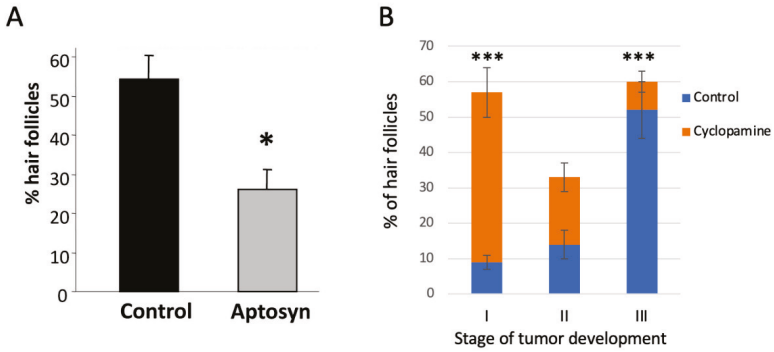

Fig. 4. The number of tumor-bearing hair follicles in mice treated with Wnt (A) and Shh (B) inhibitors
Source: made by authors

Conclusion

The data shows that Wif1 and Shh are possible targets of BMP in developing hair follicle tumors. Furthermore, Wnt and Shh signaling pathways differentially participate in the initiation and progression of tumors when inhibiting the BMR signal. Thus, the BMP signaling pathway functions as tumor suppressor via, at least in part, antagonistically regulating Wnt and Shh pathway activities in skin epithelial cells.

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Роль сигнальных систем Wnt и Shh в ноггин-индуцированном туморогенезе

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Аннотация. Взаимодействие между сигнальными путями BMP, Wnt и Shh при развитии эпителиальных опухолей кожи остается малоисследованным. Для изучения роли Wnt и Shh в развитии опухолей кожи мы использовали трансгенную мышиную модель, экспрессирующую ноггин (антагонист BMP) в эпителии кожи и приводящую к развитию опухолей волосяных фолликулов. Сравнительный анализ экспрессии генов и белков показал повышение активности сигнальных систем Wnt и Shh в коже трансгенных мышей на различных стадиях развития фолликулярных опухолей. Кроме того, рекомбинантный BMP-4 подавляет экспрессию Shh в культуре опухолевых клеток, в то время как фармакологические ингибиторы Wnt и Shh значительно замедляют формирование и развитие опухолей у трансгенных мышей, экспрессирующих ноггин. Эти результаты расширяют наши знания о роли факторов роста в канцерогенезе и могут привести к нахождению новых мишеней для специфических терапий онкологических заболеваний.

Ключевые слова: сигнальные пути BMP, ноггин, опухоли, кожа, трансгенные мыши

Заявление о конфликте интересов: Авторы заявляют об отсутствии конфликта интересов.

История статьи: поступила в редакцию 20 июля 2022 г., принята к публикации 13 ноября 2023 г.

Для цитирования: *Mardaryev A.N., Mardaryev N.S., Mardaryeva N.V., Schiptsova N.V.* The role of Wnt and Shh signaling systems in noggin induced tumorigenesis // Вестник Российского университета дружбы народов. Серия: Агрономия и животноводство. 2024. Т. 19. № 1. С.165–175. doi: 10.22363/2312-797X-2024-19-1-165-175

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