Int. J. Dev. Biol. 56: 279-283
doi: 10.1387/ijdb.113397lh

THE INTERNATIONAL JOURNAL OF DEVELOPMENTAL BIOLOGY
www.intjdevbiol.com

MMTV-neu mice deficient in STAT1 are susceptible to develop ovarian teratomas

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ABSTRACT Signal transducer and activator of transcription 1 (STAT1) serves in the protection of the organism against pathogens and other harmful insults. It is implicated in innate immune response, immunosurveillance, tumor-suppression, and the response to genotoxic as well as oxidative stress. We report here that 9 of 140 examined STAT1 deficient mouse mammary tumor virus-neu (MMTV-neu) mice developed differentiated ovarian teratomas, which histologically resemble benign dermatoid cysts. Conventional karyotyping revealed diploidy without structural rearrangements of the chromosomes. STAT1 proficient MMTV-neu mice with the same genetic background (FVB/N), and STAT1 deficient C57BL/6 mice failed to develop this type of tumor. This indicates that STAT1 deficiency promotes teratoma formation and this depends on MMTV-neu expression and/or the genetic background. Since ovarian teratomas are considered to develop as a consequence of alterations in the maturation of oocytes and follicular cells, we compared the ovaries from non-tumor bearing STAT1 deficient and proficient MMTV-neu mice. No detectable alterations in the number and proportion of the different follicular developmental stages were detected, implying the absence of non-redundant functions of STAT1 in normal folliculogenesis, as well as in follicular atresia. However, strong staining for STAT1 was detectable in granulosa and theca cells. These results point to a role for STAT1 in protecting from teratoma formation in a later step of tumorigenesis, e.g. by inducing apoptosis and eliminating premature or aberrantly formed follicles which have the potential to transform into teratomas.

KEY WORDS: *teratoma, ovary, STAT1, folliculogenesis*

Benign cystic teratomas belong to the most common ovarian tumors developing in women of the reproductive age. They are considered to stem from parthenotes, which develop from aberrant activated oocytes in the absence of fertilization (Edson *et al.*, 2009, Parrington *et al.*, 1984). Search for genetic defects facilitating the formation of teratomas in humans is impeded by the exceedingly rare frequency of familial teratomas (Nezhat *et al.*, 2010). In mice, spontaneous development of teratomas is rare and only a few reports have documented a link between the expression of a particular gene and teratoma formation. One of these genes encodes the serine kinase c-mos, which is required for meiosis II arrest in activated non fertilized oocytes. Due to failure to arrest, mos deficient mice exhibit a high frequency of parthenotes (Colledge *et al.*, 1994, Hirao and Eppig, 1997), and a small percentage of these parthenotes are postulated to transform into teratomas. Bcl-2 represents a second gene linked to teratoma formation. There, its inhibin-alpha directed over-expression in granulosa cells of the ovary (Hsu *et al.*, 1996), but not its expression in oocytes (Morita *et al.,* 1999), induces the formation of teratomas. Decreased apoptosis and enhanced follicle genesis as a result of overexpression of bcl-2 in granulosa cells is postulated to be a tumor promoting factor in this particular case. A third example is ubiquitous overexpression of the alpha and beta chains of human chorionic gonadotropin (hCG) in mice, which in the ovary leads to the formation of luteomas and subsequently to teratomas (Huhtaniemi *et al.,* 2005). In addition to these three

Abbreviations used in this paper: hGC, human chorionic gonadotropin; MMTV, mouse mammary tumor virus; STAT, signal transducer and activator of transcription.

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Accepted: 9 November 2011. *Final, author-corrected PDF published online:* 23 April 2012.

ISSN: Online 1696-3547, Print 0214-6282

genes with a defined link to teratoma formation, the mouse strain LT/Sv has been identified, which is unique in its 50% susceptibility to spontaneously develop teratomas (Eppig *et al.*, 1977, Stevens and Varnum, 1974). LT/Sv mice exhibit metaphase I arrest of meiosis I, which is necessary but not sufficient for teratoma formation (Eppig *et al.*, 1996). A gene locus on chromosome 6 designated Ots1 was mapped by linkage analysis (Lee *et al.*, 1997) as responsible for teratoma formation, however the actual gene involved has not been identified yet. Interestingly, the same gene locus co-mapped with one of the loci linked with lymphocyte infiltration of mouse lung tumors and interferon production in mixed lymphocyte reactions (Lipoldova *et al.*, 2010).

We have now identified STAT1 as a fourth gene linked to the formation of benign cystic teratomas of the ovary. It encodes an inducible transcription factor, and mediates the intracellular response to type I and type II interferons (Schindler and Plumlee, 2008). Thereby it serves as an important effector in the innate immune response (Durbin *et al.*, 1996) and a key modulator of cell death (Kim and Lee, 2007). Deletion of STAT1 has been already previously described to enhance or accelerate the formation of other types of tumors (Bromberg, 2002, Klover *et al.*, 2010). One postulated mode of action by which STAT1 can protect against tumor formation is its participation in tumor immunosurveillance (Dunn *et al.*, 2006). Furthermore, it has been shown to co-operate in the response to oncogenic and genotoxic stress with other molecules such as p53 (Townsend *et al.*, 2004).

As outlined above, the three previously identified proteins promoting (bcl-2 and hCG) or inhibiting (c-mos) ovarian teratoma formation are all involved in the development and maturation of oocytes and/or folliculogenesis. In an attempt to define a potential involvement of STAT1 in these processes, the postnatal ovarian development in STAT1 deficient and proficient mice was compared. Furthermore, expression levels of STAT1 in oocytes, granulosa cells and theca cells were determined by immunohistochemistry.

TABLE 1

INCIDENCE RATE OF TUMOR FORMATION AND LITTER SIZE IN MMTV-NEU MICE PROFICIENT AND DEFICIENT FOR STAT1

	STAT1+/+	STAT1-/-
Mice with ovarian teratoma[1,2]	0/132	9/140
Mice with mammary adenocarcinomas[1,2]	132/132	140/140
Litter size[3]	9.6 ± 2.3 (n=40)	8.2 ± 2.2 (n=45)

[1]Tumors development was monitored by weekly palpation. Mammary tumors appeared with a latency of 129 to 387 days in the case of STAT1+/+ and of 117 to 322 days in the case of STAT1-/-. Mice were sacrificed not later than 6 weeks after detection of the first mammary tumor. The difference in teratoma formation frequency between the two genotypes was significant (p = 0.0041). [2]Occurance of mammary adenocarcinomas and teratomas was verified by histological examination. [3]The mean litter size of mice without palpable tumor was determined. The difference between the genotypes was found to be significant (p = 0.0053).

Results

The FVB/N mouse strain transgenic for MMTV-neu overexpresses the rat homologue of the mouse erbB2 oncogene in mammary epithelial cells. This is because the MMTV controls expression the neu transgene via strong prolactin, progesterone and mammary specific enhancer elements (Mink *et al.*, 1992, Morabito *et al.*, 2008). As a result, MMTV-neu mice develop mammary adenocarcinomas. We used the N202 line of FVB/N MMTV-neu mice (Guy *et al.*, 1992) in the present study. A mean latency of 200 days and 100% penetrance of mammary carcinoma formation were observed (Table 1). In order to test the influence of STAT1 expression on tumor formation we generated STAT1 deficient MMTV-neu mice by mating FVB/N MMTV-neu mice with STAT1 deficient C57BL/6 mice and backcrossing into the FVB/N background. Interestingly, 9 of 140 STAT1 deficient mice developed benign cystic teratomas originating from the ovary in addition to the mammary carcinomas. Histological examinations of the nine tumors revealed a highly differentiated phenotype of the tumors characteristic for dermatoid cysts with epithelial and mesenchymal structures such as cartilage tissue, areas of keratinization and adenoid structures with secretory debris (Fig. 1). Chromosomal analysis was performed with explant cultures of two teratomas and diploidy with no indications for chromosomal aberrations was observed.

Teratoma formation did not occur in 131 examined genetically matched STAT1 proficient MMTV-neu mice (Table 1), indicating that STAT1 deficiency was a necessary prerequisite to promote the formation of this type of tumor. However, STAT1 deficiency was not sufficient, since STAT1 deficient mice with C57BL/6 background did not develop teratomas. This points to a role of the genetic background and / or expression of MMTV-neu transgene. In fact, the MMTV has been described to promote transcription of genes in other tissues than the mammary gland including the ovary (Marozkina *et al.*, 2008). In accordance, we can detect elevated levels of erbB2/

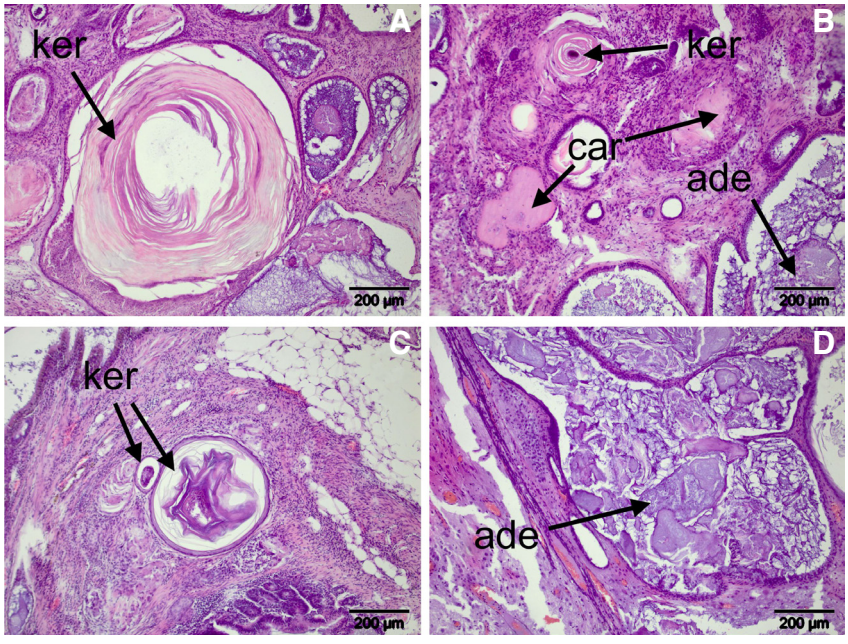

Fig. 1. Histology of MMTV-neu STAT1-/- teratomas. *Hematoxyline and eosin stained sections from four different animals are shown in Panels* **(A-D)**. *Arrows point to typical features found in differentiated teratomas such as areas of keratinization (ker), cartilage tissue (car), and adenoid structures with secretory debris (ade).*

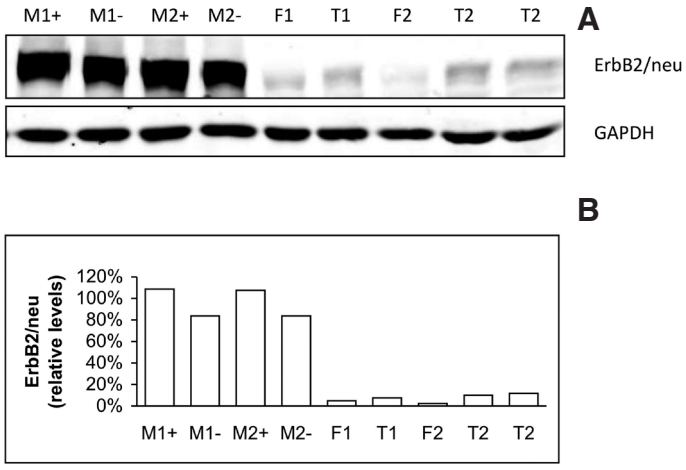

Fig. 2. ErbB2/neu expression levels in explant cultures from mammary carcinoma and teratoma tissues. *Whole cell extracts were prepared from explant cultures of teratomas (T1 and T2), mammary tumors of STAT1+/+ and STAT1-/- mice (M1+, M1-, M2+, M2-), or from fibroblast cultures of teratoma bearing mice (F1 and F2). ErbB2/neu and GAPDH expression was determined by immunoblotting* **(A)**. *Expression levels were quantified by Odyssey densitometry, and are shown relative to the expression of GAPDH for each explant culture* **(B)**. *The average expression in explants from mammary tumors was taken as 100%. In comparison to that, the average ErbB2/neu expression in teratoma cultures was 9.8 ± 1.1% and in fibroblast cultures 3.7± 1.1%.*

neu in explant cultures of teratomas when compared to fibroblast cultures. However, in comparison to mammary adenocarcinomas, expression was found to be low (Fig. 2).

Previous research has identified aberrant folliculogenesis/atresia and defects in development and activation of oocytes as early steps in the formation of teratomas. As shown in Fig. 3, STAT1 is expressed both in granulosa as well as theca cells of the ovary, whereas no specific staining was found in oocytes. Thus loss of expression might lead to defects in normal ovarian development. However, histological examination of the ovaries of 2 months, 4 months and 6 months old STAT1 deficient and proficient MMTV-neu mice for changes in the abundance of follicules with different stages of development revealed no discernable differences. Furthermore, both STAT1 deficient and proficient mice are fertile and exhibit only a small difference in the average litter size (Table 1). This indicates a requirement for STAT1 to protect against the formation of teratomas at a later step of tumorigenesis.

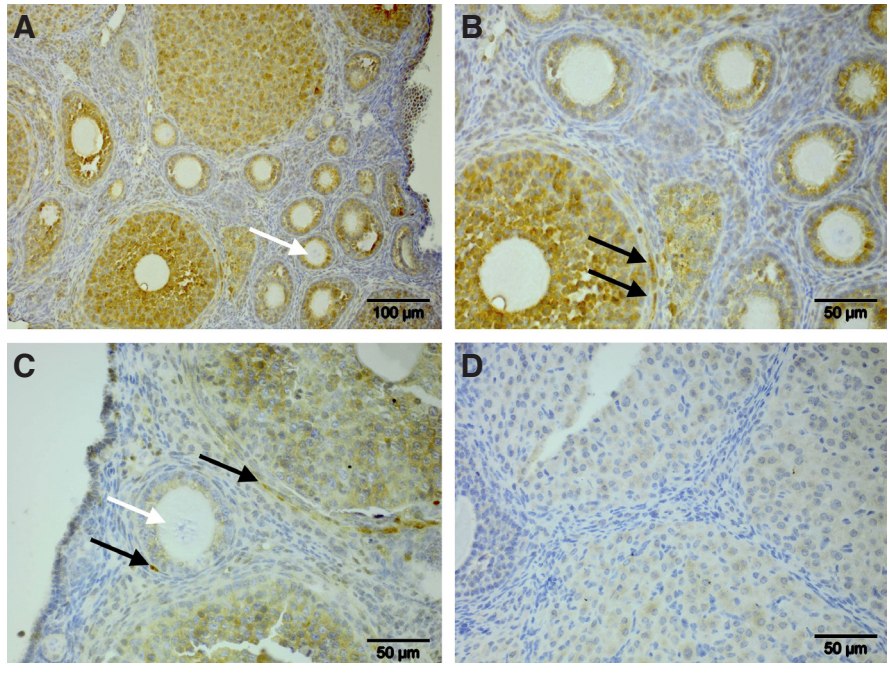

Fig. 3. Expression of STAT1 in theca and granulosa cells of the ovary. *Immunohistochemical stainings of paraffin fixed tissues are shown for FVB/N w.t.; two month old,* **(A,B)** *and MMTV-neu STAT1+/+ mice; six month old* **(C)**. *The ovary of a STAT1 deficient MMTV-neu mouse (six month old) served as a negative control* **(D)**. *Granulosa cells from primary follicles and the later stages of follicular development stained positive for STAT1. Black arrows point to selected theca cells, which are strongly positive for STAT1. Oocytes did not specifically stain for STAT1 (white arrows).*

Discussion

Our study describes STAT1 as a second gene where deletion of a gene promotes the development of benign cystic teratomas. Opposite to the deletion of c-mos, where teratomas develop subsequently to a gross defect in oocyte maturation and a high frequency of parthenotes (Colledge *et al.*, 1994, Hirao and Eppig, 1997), STAT1 deficiency was not accompanied by detectable defects in oocyte maturation. Immunohistochemical staining of STAT1 in granulosa cells and theca cells was observed. No specific staining for STAT1 in oocytes was detectable by this method. However, as shown in a previous investigation on STAT1 expression in isolated mouse oocytes, STAT1 is also expressed in this cell type (Truchet *et al.*, 2004). Since STAT1 deficient mice exhibited normal folliculogenesis and are fertile, the protein appears to have no or a redundant role in the normal ovarian development and fertilization. STAT1 might be however required for protecting against aberrant folliculogenesis and/or elimination of premature activated oocytes or parthenotes, which can spontaneously form at low frequency. This would be in accordance with the previously identified function of STAT1 as a key regulator of apoptosis (Kim and Lee, 2007) and as a tumor-suppressor (Bromberg, 2002).

The promotion of teratoma formation by STAT1 was dependent on the mouse strain. Expression of erbB2/neu in teratomas or precursor parthenotes could contribute to tumor development. Furthermore, it is well known that the genetic background can influence the development of tumors (Davie *et al.*, 2007, Rowse *et al.*, 1998) including teratomas (Lee *et al.*, 1997). However, it has to be pointed out that for FVB/N w.t. mice spontaneous formation of teratomas was never observed by us or has been described to our knowledge in the literature. This is also true for aging FVB/N mice, which can spontaneously develop tumors with a frequency of 26% and 60% after 14 month and 24 month of age, respectively, but do not form teratomas (Mahler *et al.*, 1996).

STAT1 deficiency has been shown to function as a tumor suppressor by immune cell dependent (Kaplan *et al.*, 1998) and

independent mechanism (Klover *et al.*, 2010). However, there are also examples for tumor promoting effects (Kovacic *et al.*, 2006, Schultz *et al.*, 2010). The observed protective function of STAT1 in inhibiting or eliminating the formation of teratomas is another case for the action of this transcription factor as a tumor-suppressor. Since the formation of teratomas occurs at low penetrance in STAT1 deficient mice and the initial steps of transformation occur early before teratomas can be detected by palpation, elucidation of the exact mechanism by which STAT1 acts in protecting against teratoma formation will remain a difficult task.

Materials and Methods

Mice

All animal studies were conducted in accordance with the Austrian animal welfare law and animal experiment act (BGBl. no. 501/1989 i.d.g.F) and were performed under a Committee of Animal Care of the Austrian Federal Ministry of Science and Research approved protocol. FVB/N-MMTVneu transgenic mice with the unactivated form of neu (Guy *et al.*, 1992) were purchased from Jackson Laboratory (Bar Harbour, ME). STAT1$^{-/-}$ mice in the C57BL/6 background (Durbin *et al.*, 1996) were provided by Dr. Thomas Decker. STAT1$^{-/-}$ mice were backcrossed into the FVB/background by marker-assisted backcrossing (MAX-BAX^{SM}, Charles River Laboratories, Wilmington, MA) and mice with an FVB/N background of > 98% were used for the experiments shown.

Explant cultures and chromosomal analysis

Mice were sacrificed and teratomas as well as control tissue (ear) excised and cut into small pieces. Cultures of explants grown for four weeks in DMEM/F12 supplemented with 10% heat inactivated FCS, 200 mM L-glutamine, 5 μg/ml insulin, 10 ng/ml EGF and 1 μg/ml hydrocortisone were used for the determination of erbB2 levels in cell extracts as well as for the preparation of metaphase arrested cells for chromosomal analysis. Explant cultures from MMTV-neu tumors were prepared as described (Parajuli and Doppler, 2009).

Immunoblotting, imunohistochemical analysis

Antibodies for immunoblotting were anti-erbB2/neu (SC-284; Santa Cruz Biotechnology; 1:1000) and anti-GAPDH (1:8000; MAB374; Chemicon). Proteins from total cell extracts were separated on 8% SDS-PAGE and immunoreactive bands detected and quantified by Odyssey Infrared Imaging (LICOR, Biosciences) as described (Haffner *et al.*, 2008). STAT1 immunohistochemistry was performed on paraffin-embedded sections with SC-346 antibody (Santa Cruz Biotechnology; 1:1000, 1hr R.T.) and the Rabbit-on-Rodent HRP-Polymer (Biocare Medical) as a secondary detection system. Tissues were counterstained with hematoxylin.

Statistical analysis

Differences in teratoma formation frequency were evaluated with the two-sided Chi^2 test and differences in litter size were compared by the two-sided T-test.

Acknowledgments

We would like to thank Mrs. Martina Chamson, Mrs. Stefanie Faserl and Mr. Anto Nogalo for excellent technical assistance, and Dr. Karl Illmensee for helpful discussions. This work was supported by the Integrated Center for Research and Therapy (IFTZ) of Innsbruck Medical University.

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