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Visions & Reflections (Minireview)

What leads from *dead-end?*

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Abstract. The 129 mouse strain develops congenital testicular germ cell tumors (TGCTs) at a low frequency. TGCTs in mice resemble the testicular tumors (teratomas) that occur in human infants. The genes that cause these tumors in 129 have not been identified. The defect at the *Ter* locus increases TGCT incidence such that 94 % of 129-*Ter/Ter* males develop TGCTs. The primary effect of the *Ter* mutation is progressive loss of primordial germ cells (PGCs) during embryonic development. This results in sterility in adult *Ter*/*Ter* mice on all mouse strain backgrounds. However, on the 129 background, *Ter* causes tumor development in addition to sterility. Therefore, *Ter* acts as a modifier of 129-derived TGCT susceptibility genes. *Ter* was identified to be a mutation that inactivates the *Dead-end1* (*Dnd1*) gene. In this perspective, I discuss the possible areas of future investigations to elucidate the mechanism of TGCT development due to *Dnd1* inactivation.

Keywords. *Ter*, *dead-end*, *Dnd1*, testicular germ cell tumors.

The 129 mouse strain is genetically predisposed to develop spontaneous, congenital testicular germ cell tumors (TGCTs) that resemble the tumors that occur in the testes of human infants (pediatric germ cell tumors or testicular type I germ cell tumors) [1, 2]. Approximately 10 % of the 129 males develop TGCTs [3]. However, susceptibility genes from the 129 strain that cause these tumors have not been identified. The defect at the *Ter* locus [4] increases TGCT incidence such that 94 % of 129-*Ter/Ter* males develop TGCTs [5]. The primary effect of the *Ter* mutation is progressive loss of primordial germ cells (PGCs) during embryonic development. This results in sterility in adult *Ter*/*Ter* mice on all mouse strain backgrounds. Tumor development due to *Ter* occurs only on the 129 background. Therefore, *Ter* acts as a potent modifier of 129-derived germ cell tumor susceptibility genes. Using genetic mapping and positional cloning approaches, *Ter* was identified as a point mutation that inactivates the *Dead-end1* (*Dnd1*) gene on mouse chromosome 18 [6, 7]. The coding region of the *dead-end* gene in the *Ter* strain is disrupted by a nonsense mutation. In this perspective, I discuss some observations regarding germ cell tumor development in the 129-*Ter* mice to reflect on the possible areas of future investigations to elucidate the mechanism of TGCT development due to *Dnd1* inactivation.

Germ cell tumors are one of the few cancer types in which the cancer stem cell of origin has been identified. In mice, experimental evidence indicates that germ cell tumors arise from primordial germ cells (PGCs) [8] that become transformed into embryonal carcinoma (EC) cells (Fig. 1). Noguchi and Stevens observed foci of EC cells in embryonic day 16 (E16) fetuses of the 129-*Ter* strain and in E15 fetuses of the 129 strain [9]. Further light microscopy studies at higher magnifications of serially sectioned gonads also identified EC cells within the testis cords at E14 [10] of the 129-*Ter* strain. This suggested that teratocarcinogenesis likely starts 2 – 3 days earlier at around E12.5.

The EC cells were observed to be enclosed by the sex cords of the developing gonads, and thus the tumors arose from PGCs (also referred to at this stage as gonocytes) within the sex cords (or developing seminiferous tubules). In some tumors, EC cells occupied interstitial areas of the embryonic testes and were continuous with the seminiferous epithelium. This indicated invasive rupture of the testis cord basement membrane. They also observed normal gonocytes and atypical gonocytes with syncytial masses interspersed with the EC cells [10]. Generally, EC cells proliferate until after birth. But soon after that, most EC cells differentiate randomly into adult and embryonic tissues that constitute the tumors (Fig. 1).

Linking PGC loss to transformation in *Ter*

Primarily, *Ter* causes depletion of PGCs that starts during embryonic development and leads to postnatal sterility [5]. Tumor development due to *Ter* is a strain-specific phenomenon in that germ cell tumor development (together with sterility) occurs only on the 129 strain background. This observation in 129-*Ter* links PGC death to PGC transformation [4, 5, 11, 12], and the question is why inactivation of *Dnd1* increases the susceptibility of PGCs to transform.

PGC death in the *Ter* mouse strain has been observed to be a gradual process. Normally, mouse PGCs are first observed at E7.5 at the base of the allantois [13–15]. At E8.5, PGCs begin to migrate through the hindgut and dorsal mesentery of the developing embryo and arrive at the fetal gonads (or genital ridges) at E10.5 [16–18]. During migration, as well as after arrival and colonization of the genital ridges, PGCs proliferate and increase in number until E13.5 [19]. At around E12, the Sertoli cells of the embryonic male genital ridge begin to aggregate around clusters of PGCs to initiate development of the testis cords (reviewed in [20]). After E13.5, PGCs in male gonads undergo mitotic arrest and remain arrested until after birth [14]. Sakurai observed that C57Bl/6J-*Ter* strain embryos had the same number of germ cells at E7.5 as wild-type but the numbers declined gradually from E8.5 until E12.5 when PGCs are migrating and proliferating [21]. We introduced a transgene (*GOF-1/ΔPE/EGFP)*, GFP (green fluorescent protein) driven by the germ-cell-specific Oct-4 promoter, into the 129-*Ter* mouse, as a marker for PGCs. We found that at E12.5, although there were significantly fewer germ cells in 129-*Ter* mice, the few germ cells appeared to be migrating towards the genital ridges [6]. Sakurai also reported that the PGC migration appeared to be unaffected in the *Ter* mice [21]. Moreover, tumors in the *Ter* males are always observed to develop in the embryonic gonads or in adult testes. The reason for PGC loss in the *Ter* strain is not clear.

Direct or indirect effects of *Dnd1* inactivation on PGCs

Why does inactivation of *Dnd1* promote PGC transformation? One possible scenario is that inactivation of *Dnd1* in PGCs may in some way cause genetic or epigenetic 'damage' to the cells. Most of the 'damaged' PGCs die during migration, but a subset of the PGCs escape death and reach the developing genital ridges. These PGCs survive to become enclosed within the developing testis cords to transform into EC cells.

The idea that PGCs may suffer damage comes from examining the mouse *Dnd1* encoded protein, DND1. The most prominent motif in DND1 is an RNA recognition motif (RRM). The mouse DND1 protein shows highest homology to mouse ACF (APOBEC-1 complementation factor) [6, 7]. ACF is the RNA-binding co-factor of APOBEC-1, and together they comprise the RNA editing enzyme complex (editosome) [22, 23]. APOBEC-1 together with ACF converts specific cytidines to uridines in the apolipoprotein B transcript and other messenger RNAs (mRNAs) [24]. Based on this observation, it is possible that DND1, like ACF, may be a co-factor of other APOBEC-like proteins, and DND1 may be involved in nucleic acid editing.

APOBEC proteins are present in vertebrates from zebrafish to man [25]. Members of the family have zinc-binding domains with homology to bacterial cytidine deaminase. There are five *Apobec* genes in the mouse: *Apobec*-1, *Apobec*-2, *Apobec*-3, *AICD* (Activation-induced cytidine deaminase or *AID*) and a newly identified gene *Apobec*-4 [26]. Aberrant expression of APOBECs have been proposed to cause promiscuous nucleoside and nucleotide modification, and, genomic instability [27]. Human APOBEC-1 and 3 exhibit potent DNA mutator activity in *Escherichia coli* assays [28]. They trigger DNA mutation through dC deamination, and each protein exhibits distinct target sequence specificity. The results reveal the APOBECs to be a family of potential active dC/dG mutators, with possible implications for cancer.

One possibility is that DND1 regulates a similar deaminase/editing activity, and this is deregulated in PGCs lacking *Dnd1*. This may result in damage to DNA or RNA of PGCs. For example, one can envision damage or mutations in tumor suppressors leading to their inactivation, and this would promote PGC transformation.

A second possibility is that *Dnd1* loss leads to tumor development in an indirect manner. So far, inactiva-

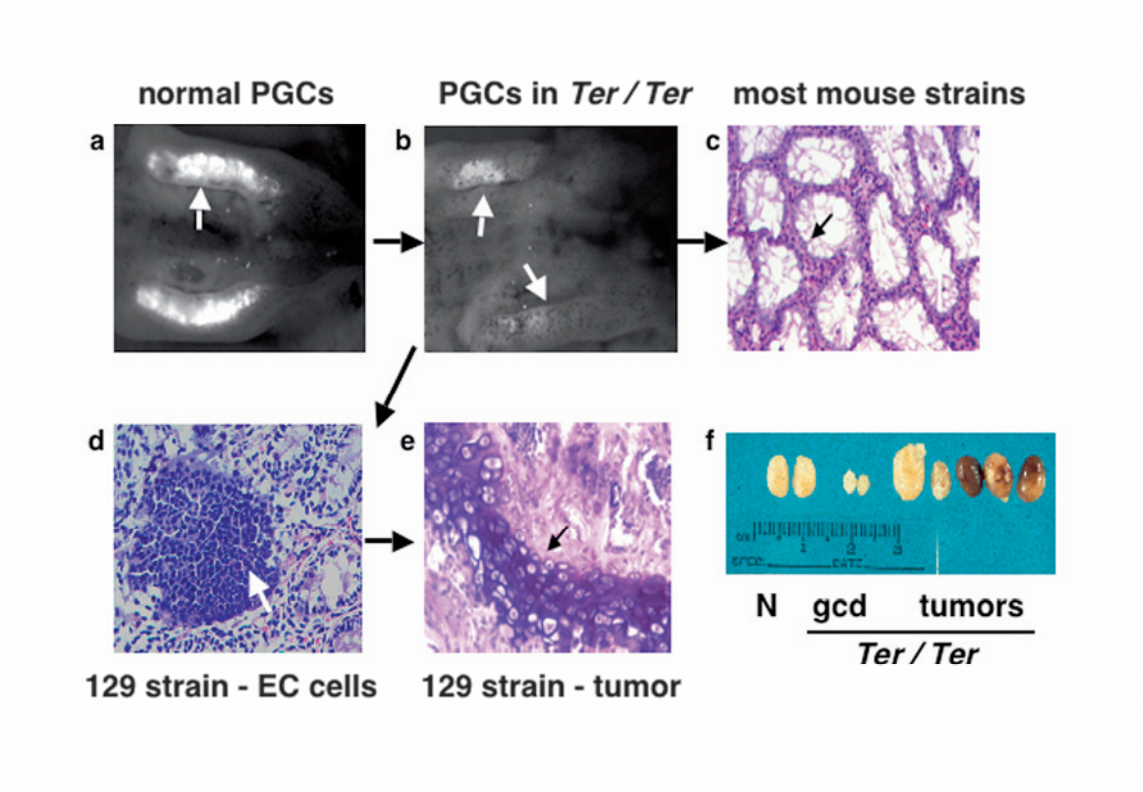

Figure 1. Development of testicular germ cell tumors in *Ter/Ter* mice. (***a***) Primordial germ cells (PGC) (white arrow) in normal genital ridges of E12.5 embryos. The PGCs express GFP (green fluorescent protein) from the Oct4 promoter [6]. A few PGCs are still found outside the genital ridges. (***b***) PGCs (GFP-expressing, indicated by white arrows) are progressively lost in *Ter/Ter* mice and significant reduction in numbers is observed at E12.5. (***c***) Loss of PGCs renders adult *Ter/Ter* mice sterile. Arrow indicates lack of adult germ cells in histological section of adult *Ter/Ter* testes. (***d***) Transformation of dying PGCs to embryonal carcinoma cells (EC) (white arrow) observed in a histological cross-section of newborn testes from the 129 strain. (***e***) EC cells differentiate into adult and embryonal cells in testicular tumors (arrow indicates cartilage in tumor). (***f***) Comparison of normal testes (N), sterile, germ cell deficient testes of *Ter/Ter* mice (gcd) and germ cell tumors from 129-*Ter/Ter* (tumors) mice.

tion of *Dnd1* has been shown to affect PGC survival in zebrafish and mouse PGCs [6, 29], but the mechanism for PGC loss has not been elucidated. *Dnd1* may influence PGC survival through some mechanism other than interaction with the APOBECs. The net result in *Ter* strains would be that when fewer PGCs arrive at the genital ridge, these come under the influence of growth factors secreted by the somatic cells of the genital ridge (reviewed in [30]). The level of growth factors would likely be in excess to the number of PGCs, and that may result in unchecked proliferation and transformation into EC cells.

Role of somatic environment of the male genital ridge in tumor development

As tumors in the 129-*Ter* strain are only seen in the developing gonads and testes of males, this suggests that the developing gonads of the 129 strain, between E12.5 and E15.5, provide a suitable environment to allow transformation of PGCs from *Ter*. The importance of the somatic environment for PGC transformation is supported by the dissociation-reaggregation experiments carried out by Renegass et al. [31]. They separated the germ cell fraction from the somatic cell fraction of gonads isolated from E12.5 to E17.5. The germ cells and somatic cells were then reaggregated and implanted in adult testes, where they formed seminiferous tubules with teratomas. They observed low incidence of teratomas when E12.5 PGCs from tumor-susceptible strains were combined with somatic cells from E15.5 or E17.5 tumor-susceptible strains, indicating that the age of the somatic cells was important for tumorigenesis. E12.5 PGCs from susceptible strains combined with E12.5 somatic cells from tumor-resistant strains formed tumors with high incidence. However, E12.5 PGC from tumor-resistant strains combined with somatic cells from susceptible strains did not form tumors. Thus, only PGCs from strains with genetic susceptibility for tumor development formed tumors in the dissociation-reaggregation

experiments. These experiments highlight that both PGC intrinsic factors (in this case, inactivation of *Dnd1*) as well as PGC extrinsic factors (somatic cells of the genital ridge) are important for germ cell tumor development.

During migratory stages, when PGCs are in the developing hind-gut and dorsal body wall and organs surrounding the gonad, the 129-*Ter* PGCs (as observed by Sakurai and us) do not transform or develop into tumors in these environments through which they are migrating. Thus, *Dnd1* inactivation in PGCs of 129 strain is not sufficient for transformation. Moreover, tumors have not been observed in ectopic sites even on the germ cell tumor-susceptible 129 background. This is in contrast to that in humans, where almost half of pediatric germ cell tumors occur as extragonadal germ cell tumors, and these are thought to arise from mislocalized PGCs that fail to die at these ectopic sites [32, 33]. In mice, the pro-apoptotic gene *Bax* has been shown to be required for the death of ectopic PGCs [34]. However, in the 129-*Ter* strain the death of ectopic PGCs is unaffected.

Most of the germ cells of the female *Ter* mice also die [4, 9] (because of lack of *Dnd1*). But again tumors do not develop, and therefore the female gonadal environment also does not support TGCT development. Thus, in the *Ter* strain, the susceptible PGCs when present within the milieu of the developing male gonad are able to transform to EC cells. This suggests that factors from the 129 male gonadal environment provide the right environment for some of the PGCs to survive and transform to EC cells.

What possible environmental factors result in transformation of these damaged PGCs? Among the suspects would be individual or synergistic effects of the autocrine, paracrine growth factors and hormones secreted by the somatic cells of the male genital ridges at the E11.5–E15.5 stages. These factors could include *kit* ligand (or stem cell factor), LIF (leukemia inhibitory factor), retinoic acid, FGF2 (fibroblast growth factor) (reviewed in [30]) or other unknown growth factors. Between E11.5–E12.5, the male genital ridge undergoes morphological and cellular changes to organize the testis structure (reviewed in [20]), which includes compartmentalization of the testis into testis cords and differentiation of the Sertoli and Leydig cells. It is possible that factors involved in these processes may indirectly serve to transform susceptible PGCs. One way to test the effects *in vivo* of any putative transforming factor (*f*) would be to cross the 129-*Ter* mouse strain with mice with deficiency of the factor (*f*−/− mice). Mice homozygous for *Dnd1* inactivation (*Ter*/*Ter*) and the factor (129-*Ter*/*Ter*; *f*−/−) should have reduced incidence of testicular germ cell tumors.

To summarize, PGCs 'damaged' due to *Dnd1* inactivation become susceptible to transformation under the influence of somatic factors from the male genital ridges. On the other hand, *Dnd1* inactivation may cause the reduced number of PGCs to aberrantly proliferate and transform because they come under the influence of disproportionate levels of somatic factors from the male genital ridges.

Strain specificity of tumor development

Another puzzle is why tumors in the genital ridges occur only on the 129 strain background. When *Ter* is on other mouse strain backgrounds, the PGCs die and transformation to EC cells is not observed. One possibility is that factors produced by the somatic cells of the 129 strain genital ridge may be qualitatively or quantitatively different and may more likely induce tumorigenesis compared to those found in other mouse strains. Another possibility is that the timing of growth factor release may be different in 129 genital ridges compared to that in other mouse strains, such that the prolonged expression of a specific factor may render the 'damaged' PGCs susceptible to transformation. An example of strain-specific difference is that, for reasons not understood, PGCs from strains with increased TGCT incidence such as 129-*Ter* show prolonged mitotic activity that lasts up to E15 [9].

In addition, in the 129, there may be some PGC intrinsic defect/attenuation of tumor suppressor (TS) or apoptotic activity such that PGCs from the 129 fail to execute the cell death response upon damage to its cellular components due to *Dnd1* absence. One way to address this would be to compare the genes and microRNAs [35, 36] involved in the TS and apoptotic response pathways that play critical roles at around E10.5–E13.5 (after PGCs have entered and colonized the genital ridges) in 129-derived PGCs compared to those in other strains. As TGCTs in mice develop between E11.5 and E13.5, the role of specific TSs at these stages must be required to prevent PGC transformation. Deficiency of two well-studied TSs, p53 [37] and PTEN [38], causes TGCT in mice. The role of these TSs in PGCs are not entirely clear. One study indicates that the zinc-finger transcription factor Zfp148 is involved in regulating and stabilizing p53 in PGCs and may have a role in promoting cell cycle arrest of PGCs at around E13.5 [39]. Deletion of PTEN in PGCs causes transformation into EC cells more readily [38]. Interestingly, the activity of the tumor suppressor PTEN in PGCs can be downregulated in response to estrogens secreted by somatic cells of the gonad [40]. This is intriguing, because in humans exposure to estrogens *in utero* has been

implicated as one possible cause for the increase in testicular cancer incidence in young males [41, 42].

Conclusions

In summary, although inactivation of *Dnd1* increases incidence of TGCTs in 129 strain mice, loss of *Dnd1* alone is not sufficient for PGC transformation. Other PGC intrinsic and extrinsic factors likely play critical roles for the transformation of PGCs. Autocrine or paracrine growth factors secreted by the male somatic cells of the developing mouse gonad at around E11.5–E15.5 may induce the few dying PGCs in the 129-*Ter* mouse embryo to transform; or factors specific to the 129 strain, either PGC intrinsic or present in the male 129 gonadal somatic tissues, may induce transformation.

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