How the TRAMP Model Revolutionized the Study of Prostate Cancer Progression

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See related article by Gingrich et al., Cancer Res. 1996;56:4096–102.

FDA approval for prostate-specific antigen (PSA) testing in 1994 as a screening aid led to a dramatic increase in the diagnosis of prostate cancer cases. Yet, researchers had few tools to study this disease beyond a handful of human cell lines (mainly LNCaP, PC-3, and DU145), pedigrees of rat carcinogen–enriched cell lines developed from autochthonous prostate cancer tumors (including the Dunning, Noble, and Pollard series), in vivo growths of prostate cancer/mesenchyme tissue recombinants, and human prostate cancer xenographs (such as CWR22). None of these models, however, recapitulated all the parameters of prostate cancer progression in human disease, including formation of initial hyperplasia, intraepithelial neoplasia (PIN), adenocarcinoma, metastasis to peripheral organs including local lymph nodes and bone, and recurrence from androgen deprivation therapy (1).

The few attempts to produce transgenic (Tg) mouse models of prostate cancer in the early 1990s suffered from a lack of prostate specificity (2, 3) or from use of oncogenes irrelevant to typical human prostate cancer oncogenesis (4). An early attempt to increase prostate specificity, by using the PSA promoter to drive expression of a Ras oncogene, paradoxically did not cause prostate cancer, but rather cancer of the salivary glands and gastrointestinal tract (5). This changed, however, in 1994 when Maroulakou and colleagues (6) described Tg mice expressing the SV40 T-antigen (Tag) driven by the rat prostatic steroid binding protein C3 gene promoter. These mice included eight independent founder lines in both C57BL/6 and FVB backgrounds. Line 5666, which exhibited low Tag immunohistochemical staining levels in the prostate epithelium as well as restricted expression to the dorsal and ventral lobes of the prostate (compared with other prostate lobes and body organs, assessed by RT-PCR), developed only epithelial hyperplasia and low-grade PIN after 33 weeks. In contrast, line 8247 exhibited PIN lesions by 10 weeks of age, hyperplasias in all prostate lobes by 22 weeks, and invasive adenocarcinomas by 20 weeks of age (14). The Cancer Research article by Gingrich and colleagues (15), where this model was first named TRAMP, followed mice over roughly 30 weeks for pathologic and immunohistochemical staining levels in the prostate epithelium and FVB backgrounds. Line 5666, which exhibited low Tag expression levels in the prostate epithelium, was strength-ened by a decade of research from Robert Matsusik’s laboratory, culminating with the observation that the −426 to +28 rPB promoter region was sufficient to drive androgen-responsive expression (9). The clinical relevance for the use of SV40-Tag, which induces oncogenic progression by binding to and inactivating the Trp53 and Rb1 tumor suppressors (10), was based on previous data showing loss of p53 and Rb in human prostate cancer (11, 12).

Because transgene chromosomal insertion sites as well as strain background were known to influence transgene expression levels and phenotypic penetrance (13), initial production of TRAMP mice included eight independent founder lines in both C57BL/6 and FVB backgrounds. Line 5666, which exhibited low Tag immunohistochemical staining levels in the prostate epithelium as well as restricted expression to the dorsal and ventral lobes of the prostate (compared with other prostate lobes and body organs, assessed by RT-PCR), developed only epithelial hyperplasia and low-grade PIN after 33 weeks. In contrast, line 8247 exhibited PIN lesions by 10 weeks of age, hyperplasias in all prostate lobes by 22 weeks, and invasive adenocarcinomas by 20 weeks of age (14). The Cancer Research article by Gingrich and colleagues (15), where this model was first named TRAMP, followed mice over roughly 30 weeks for pathologic and immunohistochemical staining levels in the prostate epithelium and FVB backgrounds. Line 5666, which exhibited low Tag expression levels in the prostate epithelium, was strength-ened by a decade of research from Robert Matsusik’s laboratory, culminating with the observation that the −426 to +28 rPB promoter region was sufficient to drive androgen-responsive expression (9). The clinical relevance for the use of SV40-Tag, which induces oncogenic progression by binding to and inactivating the Trp53 and Rb1 tumor suppressors (10), was based on previous data showing loss of p53 and Rb in human prostate cancer (11, 12).

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A provocative finding regarding the pathobiology of TRAMP mice is that poorly differentiated tumors arising in >28-week-old mice, or at a higher frequency in castrates, expressed neuroendocrine markers such as synaptophysin (21). Neuroendocrine (NE) prostate cancer is rare, comprising less than 2% of all cases, and likely arises from rare, AR-negative NE cells normally found within the basal epithelial layer in acini (22). However, at least 50% of the synaptophysin-positive TRAMP tumors also expressed AR, suggesting a potential transdifferentiation phenomenon. This phenomenon has been described in patient-derived xenograft models forced into castration-resistant (CR) growth (23), or in CR prostate cancer (PC) patients after prolonged therapy with AR antagonists (24). This may be influenced by the TRAMP strain background, because CR tumors in the FVB background seemed to be formed by NE lineage cells independent of those forming epithelial cell lesions (25, 26).

In the decade after the introduction of TRAMP mice, several groups addressed how the SV40-Tag and the nature of the PB promoter affected the incidence of prostate adenocarcinomas, NEPC, and metastases. For example, Masumori and colleagues produced a Tg model expressing only the so-called “large Tag” versus the “small t-ag” transcript included in the TRAMP construct whose expression is driven by a larger, 12 Kb PB promoter that contained additional androgen and growth factor-responsive sequences. This LPB (a.k.a. LADY) model produced PIN lesions, adenocarcinomas and metastases that expressed NE markers starting after 24 weeks, but at a much lower frequency than in TRAMP mice (27). Zhang and colleagues sought to address the fact that the TRAMP strain background is either prior to overt neoplastic onset or at a PIN stage, developed recurrent tumors that were much more poorly differentiated than the tumors arising in non-castrates (20), and castration increased the incidence of metastasis formation in the liver, salivary glands, and calvaria (21). Of note was the persistence of androgen receptor (AR) expression during disease progression to adenocarcinoma (18).

Conclusions

In the two decades since the publication describing the TRAMP model, many groups have produced multiple Tg models of prostate cancer, incorporating other well-documented changes found in human prostate cancer, such as Myc upregulation or PTEN loss. However, the TRAMP model has exhibited amazing staying power in the field, even surviving its association with NEPC, which was originally thought to relegate it to a rare prostate cancer pathology, but which is now gaining appreciation as a significant mechanism of disease progression arising from continued AR antagonist therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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