SnapShot: Genetic Mouse Models of Cancer

Cell

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Gene	Genetic Approach	Primary Tumor Types	Cooperativity Models	Clinical Significance
p53 Tumor Suppressor	*Trp53* mouse germline knockout.	*Trp53*$^{-/-}$ homozygous: 100% tumor penetrance at ~4.5 months. Typical tumors: T cell lymphoma (>60%); soft tissue sarcoma (~25%); osteosarcoma, brain tumors, teratoma (together <15%); carcinomas rarely observed. *Trp53*$^{+/-}$ heterozygous: 50% tumor penetrance at 17 months. Typical tumors: T cell lymphoma (~30%); soft tissue sarcoma (~30%); osteosarcoma (~30%); more carcinomas than *Trp53*$^{-/-}$ mice.	Oncogenic cooperativity observed between *Trp53*$^{-/-}$ and other lesions such as *Rb*$^{-/-}$ or Eμ-*Myc*. Carcinogenesis induced by different genotoxic agents or irradiation is accelerated in Trp53-deficient mice.	Mutations in TP53 found in more than 50% of all human tumors.
	Trp53 point mutation knockin mice express *Trp53* (R172H) or *Trp53* (R270H) from the endogenous locus.	Tumor spectra differ from germline *Trp53* knockout mice with more carcinomas, B cell lymphomas, endothelial tumors.	In mice, Trp53 (R172H) and Kras (G12D) cooperate to promote chromosomal instability and metastatic pancreatic ductal adenocarcinoma.	Li-Fraumeni syndrome patients have TP53 point mutations rather than deletions, so knockin mice are better models of this disease.
	Conditional *Trp53* knockout mice carry loxP sites in introns 1 and 10 of the *Trp53* locus.	Homozygous mice are not tumor prone. When crossed with mice expressing Cre in the germline, wild-type *Trp53* allele is excised and mice develop the same tumor spectrum as *Trp53* germline knockout mice.	These mice develop breast cancer when crossed with *Brca2* conditional knockout mice and *K14-Cre* mice. When crossed with *Rb1 loxP/loxP* mice, small-cell lung cancer results after treatment with Adeno-Cre and deletion of the two tumor suppressor genes.	Breast cancer is the second most frequent cause of death among US women. 1 in 27 women dies of breast cancer. Small-cell lung cancer accounts for ~20% of all lung cancers.
Ink4a/Arf Tumor Suppressors	*Ink4a/Arf* germline knockout mice carry a deletion of exon 2/3 of the *Ink4a/Arf* (*Cdkn2a*) locus eliminating both p16 (Ink4a) and p19 (Arf).	Homozygous mice develop sarcomas (50%) and B cell lymphomas (50%) by ~32 weeks. In heterozygous animals, tumors appear with lower penetrance and longer latency and uniformly demonstrate loss of the wild-type allele.	Loss of Ink4a/Arf cooperates with oncogenes expressed from tissue-specific promotors, such as tyrosinase-Ras (melanomas) and Eμ-Myc (B cell lymphomas). EGFR, if delivered in a retrovirus to glia, induces formation of gliomas in *Ink4a/Arf* homo- and heterozygous mice.	Inactivation of the *INK4a/ARF* locus is one of the most common lesions in various human tumors and can arise from homozygous deletions (14%), point mutations (5%), or promoter methylation (20%).
	Arf germline knockout mice lack p19 (Arf) due to deletion of exon 1β but express normal p16 (Ink4a).	80% of homozygous mice develop sarcomas (43%), T cell lymphomas (29%), carcinomas (17%), and neurological tumors (11%) by ~38 weeks. Tumors in heterozygous mice are less frequent and are accompanied by loss of the wild-type allele.	Like loss of Trp53, Arf deficiency accelerates tumorigenesis induced by various mitogenic oncogenes, implicating Arf as a crucial mediator of oncogene signaling and a component of a cellular failsafe mechanism that counters hyperproliferative signals.	
	Ink4a germline knockout mice lack p16 (Ink4a) but express p19 (Arf).	~25% of the homozygous mice develop tumors (mainly sarcomas and lymphomas) by ~44 weeks.	*Ink4a* knockout mice are prone to chemically induced carcinogenesis. Recent studies have implicated p16 in stem cell aging.	
Kras Oncogene	Conditional *Lox-STOP-Lox-Kras2* (*G12D*) mice (*LSL-Kras*) express an activating mutant *Kras* allele from its endogenous locus after Cre-mediated excision of a STOP cassette.	Non-small-cell lung cancer (adenocarcinoma) produced by intranasal administration of Adeno-Cre.	*Trp53* loss or mutation strongly promotes progression of Kras(G12D)-induced lung adenocarcinomas, yielding invasive desmoplastic tumors that metastasize early and resemble advanced human lung adenocarcinomas.	Adenocarcinoma is the second most common type of non-small-cell lung cancer (after squamous cell carcinoma) and has increasing incidence rates.
		Pancreatic cancer produced by crossing with *Pdx-1-Cre* transgenic mice.	Activated *Kras* and *Ink4a/Arf* deficiency cooperate to produce metastatic pancreatic ductal adenocarcinoma with similar genetics and histopathology to human pancreatic cancer.	Pancreatic cancer is fourth leading cause of cancer death in US; there is no effective treatment. Mutations in KRAS in ~90% of pancreatic cancers.
		Myeloproliferative Disease (MPD) produced by crossing with *Mx1-Cre* mice and pI-pC treatment.		Acute myeloid leukemia (AML) is associated with activating lesions in RAS signaling networks in ~60% of cases. There are 12,000 new patients/year in the US, with only a 30% cure rate.
Pten Tumor Suppressor	*Pten* germline knockout.	Homozygosity for the null *Pten* mutation results in embryonic lethality (E9.5). *Pten*$^{+/-}$ mice develop multiple tumor types (breast, thyroid, endometrium, prostate, and T cell lymphoma).	Breast carcinoma development is accelerated in *Pten*$^{+/-}$ × *MMTV-Wnt1* mice, less so in *MMTV-Wnt1* mice. Only *Pten*$^{+/-}$ × *Cdkn1b*$^{-/-}$ mice but not *Pten*$^{+/-}$ mice rapidly develop prostate carcinomas at complete penetrance. *Pten* haploinsufficiency enables tumorigenesis.	The PTEN tumor suppressor is mutated in human carcinomas (e.g., breast, prostate, and endometrium) and in glioblastoma. Cowden disease patients have PTEN mutations and increased cancer risk.
	Conditional *Pten* knockout mice (*Cre-loxP* system).	Prostate-specific knockout of *Pten* by crossing with *probasin-Cre* (*PB-Cre*) mice leads to induction of senescence, which delays development of prostate cancer (median onset after 4–6 months).	Senescence is bypassed in *PB-Cre* × *Pten loxP/loxP* × *Trp53 loxP/loxP* compound mutant mice leading to rapid tumor development after puberty.	Prostate cancer is the second leading cause of cancer-related death in US males.
Myc Oncogene	Eμ-*Myc* mice express Myc in the B cell lineage under control of the immunoglobulin heavy chain enhancer (*Eμ*).	Mice develop Burkitt-like lymphoblastic B cell lymphoma, diffuse large B cell lymphoma, and plasmacytoma at 2–6 months of age.	Oncogenic cooperativity with other lesions (e.g., overexpression of Bcl-2, loss of Arf or Trp53). This cooperativity establishes oncogene-induced apoptosis as a primary barrier against tumorigenesis and a determinant of response to treatment. Insertional mutagenesis screens using Mo-MLV in Eμ-*Myc* mice led to discovery of oncogenes such as *Bmi1* and *Pim1*.	B cell non-Hodgkin lymphoma, the most common form of lymphoma, affects ~300,000 patients in the US (40% die within 5 years). Understanding heterogeneity in treatment response is a challenge for improving lymphoma therapy.
	Conditional *tet-o-Myc* mice harbor *Myc* under control of the tetracycline-responsive element (*TRE*).	Various tumors generated by crossing *tet-o-Myc* mice with tissue-specific tet-transactivator (*tTA* or *rtTA*) mice: liver carcinoma (*LAP-tTA* mice); T cell lymphoma, acute myeloid leukemia, and sarcoma (*EμSR-tTA*); breast adenocarcinoma (*MMTV-rtTA*).	Reversible expression of *Myc* boosts understanding of oncogene addiction (tumor regression after withdrawal of the causative oncogene) and tumor dormancy (blocking of causative oncogenes allows cancer cells to survive in a nonproliferative state).	Hepatocellular carcinoma is the fifth most common cancer worldwide and the third leading cause of cancer death due to lack of treatment options.
RIP1-Tag	The *RIP1-Tag* transgene directs expression of SV40 T antigen (Tag) in β cells of the endocrine pancreas.	Sequential development of hyperplasia, angiogenic hyperplasia, adenomas, and invasive carcinomas of pancreatic islets.	Complete early penetrance plus multifocal disease enable detailed characterization of the different stages of tumor development and the role of angiogenesis.	The model is widely used for preclinical drug testing.

See online version for references.

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Genetically defined mouse models of human cancer provide a tractable experimental system for studying cancer genetics, pathology, and therapy in a physiological environment. For this SnapShot, we have selected mouse models of human cancers according to whether the models have made major contributions to understanding the function of a particular cancer gene or mechanisms of tumorigenesis (e.g., tumor suppressor p53 knockout mice and RIP-Tag mice). Whenever possible, we discuss models that accurately resemble major clinical tumor types. For more information about available models visit the website of the Mouse Models of Human Cancers Consortium (MMHCC, http://emice.nci.nih.gov).

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