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Review Article

Wnt Signaling and Synovial Sarcoma

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Abstract

Synovial sarcoma is a tumor of multipotential or partly committed stem cell origin, as evidenced by its phenotypic, spatial and molecular heterogeneity. The SYT-SSX (SS18-SSX) fusion transcript characterizes this malignancy. This most frequently is either SYT-SSX1 (SS18-SSX1) or SYT-SSX2 (SS18-SSX2). Rarely a SYT-SSX4 (SS18-SSX4) fusion occurs. Gene expression analysis demonstrated that SYT-SSX2 upregulates mediators of developmental pathways including Wnt, Notch, TGFβ, hedgehog and fibroblast growth factor in human mesenchymal stem cells. In synovial sarcoma SYT-SSX2 also directly activates canonical Wnt/β-catenin signaling in preclinical studies. The Wnt signaling pathway is activated and the downstream effector β-catenin accumulates within the nucleus in 28% - 57% of clinical cases. In a potential therapeutic advance, a small molecule Wnt antagonist LGK-974 inhibits palmitoylation of Wnt by targeting the membrane bound acyltransferase Porcupine. Palmitoylation is a requirement for Wnt ligand availability. Potential future molecular treatment strategies include Wnt pathway antagonism, optimization of pathway inhibition by combinatorial therapeutics and integrating Wnt inhibition with other therapeutics such as fibroblast growth factor receptor inhibitors.

Keywords: Palmitoylation; Wnt; Synovial sarcoma; Acyltransferase

Abbreviations

Dkk: Dickkopf; LKB1: Serine/threonine protein kinase II; AMPK: Adenosine Monophosphate-Activated Protein Kinase; RNF43: Ring Finger Protein 43; SSX: Synovial Sarcoma X breakpoint; LEF: Lymphoid Enhancer-binding Factor; TCF: T-Cell Factor; NF-1: Neurofibromatosis type 1; MPNST: Malignant Peripheral Nerve Sheath Tumor; FGF: Fibroblast Growth Factor; FGFR: Fibroblast Growth Factor Receptor; EGFR: Epidermal Growth Factor Receptor; ERBB2: Human Epidermal Growth Factor Receptor 2; RAR: RA Receptor; SMO: Smoothened; LEF: JAG1: Jagged 1; IGF2: Insulin like Growth Factor 2; APC: Adenomatous Polyposis Coli; GSK3β: Glycogen Synthase Kinase-3 β; CK1: Casein Kinase 1; BRG1: Brahma Related Gene 1, LRP: Lipoprotein Receptor-Related Protein; Wnt: Wingless-Type MMTV integration site family member; YAP: Yes Associated Protein

Synovial Sarcoma

Synovial sarcoma is a mesenchymal tumor that arises from multipotential stem cells [1,2]. This is consistent with spatial variation in tumor location and phenotypic heterogeneity. Tumor characteristics include both those of myogenic and neural progenitor/precursor cells [3,4].The phenotypic plasticity and unlimited replicative potential of synovial sarcoma infers a multipotent mesenchymal stem cell of origin, a postulate supported by in-vitro experiments. A recurrent translocation involving chromosomes X and 18, t (X;18) (p11.2;q11.2) characterizes synovial sarcoma and leads to the formation of a fusion protein SS18-SSX identified in 95% of cases. This fuses SS18 a transcriptional co-activator with one of 3 homologous transcriptional co-repressors (SSX1, SSX2, SSX4). In one third of synovial sarcomas SSX18-SSX is the sole cytogenetic abnormality [5].

The fusion protein SS18-SSX is important for the initiation and progression of synovial sarcoma. Histologically synovial sarcomas are either of monophasic morphology consisting of spindle cells or biphasic morphology containing a mixture of spindle cells with cells of epithelial differentiation. Occasionally it may mimic other tumors. Differentiation of biphasic synovial sarcoma from biphasic mesothelioma is assisted by identifying mucicarmine-positive, hyaluronidase and diastase resistant mucin in synovial sarcomas, differential staining of calretinin, Ber-Ep4 and bcl-2 in mesothelioma and variation in expression of apoptotic stains [6]. A poorly differentiated variant of synovial sarcoma occurs rarely. Mutations in E-cadherin are a possible determinant of morphologic subtype of synovial sarcoma [7].

SS18-SSX epigenetically alters gene expression levels in synovial sarcoma by modifying chromatin structure through interaction with components of the Switch/Sucrose Non-Fermentable Complex (SWI/SNF) and Polycomb. SWI/SNF is a nucleosome (a DNA segment wound around 8 histone protein cores) remodeling complex, which affects gene expression. It is mainly comprised of an aggregate of associated proteins products of the SWI and SNF gene families. Polycomb group proteins are a family of proteins that epigenetically silence genes by modifying chromatic remodeling. The fusion protein is antagonistic to SWI/SNF and Polycomb.

Mechanisms of epigenetic modification include deregulated histone methylation, acetylation, and promoter methylation. In a comprehensive genome-wide analysis SS18-SSX was recruited in particular to sites modified by Polycomb that are enriched with trimethylated histone H3 on lysine 27 (H3K27me3) [8]. This usually increased or decreased gene expression levels. Hierarchical and functional clustering identified a cluster of neuronal genes densely covered by H3K27me3, which were upregulated. This substantiates

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the concept of SS18-SSX2 reprogramming gene expression towards the neural lineage. As well as the reprograming of differentiation SS18-SSX2 activated selected signaling pathways that have roles in stem cell maintenance and fate allocation. This later group includes WNT/β-catenin signaling [9].

The Wnt pathway and therapeutic targets

Wnt signaling is an evolutionary conserved pathway that participates in embryonic lineage designation, tissue stem cell renewal and homeostasis. It is constitutively activated in numerous types of cancer including colorectal cancer [10,11]. Wnt ligands are glycoproteins rich in cytosine of which there are 19 different types in mammals. Wnt binding to its receptors Frizzled and LRP5/6 causes disruption of the β-catenin degradation complex. Structural components of this destructive Axin-scaffold protein complex include APC, AXIN, glycogen synthase kinase 3 (GSK3β) and casein kinases 1 (CK1α, δ and ε) [12]. Casein kinase 1 phosphorylates β-catenin at serine 45. In usual circumstances Wnt ligand is absent and the degradation complex targets β–catenin for proteosomal degradation. In the alternative scenario, when Wnt ligand is present there is cytoplasmic accumulation of β-catenin with consequent nuclear translocation of β-catenin. This then complexes with LEF/TCF and alters gene expression.

Wnt ligands comprise 350-400 amino acids and are subject to lipid modification termed palmitoylation. Porcupine is a membrane bound O-acyltransferase that catalyzes acylation of a serine residue and subsequent post-translational palmitoylation of Wnt ligands. Most Wnt ligands are glycosylated and have lipid modification within the endoplasmic reticulum prior to transport to the Golgi apparatus [13]. Wnt ligand is palmitoylated prior to engagement with Wntless a chaperone molecule that facilitates Wnt's progress through a secretory pathway. This involves transport from the trans-Golgi network to the plasma membrane from which Wnt is secreted. Secreted Wnt ligand attaches to the Frizzled receptor. Therefore when palmitoylation is absent there is intracellular accumulation of Wnt and absent Wnt signaling. Porcupine is a founding member of a 16-gene family of membrane-bound acyltransferases with multiple membrane spanning regions. Two other members of the family also have protein substrates. These are Hhat, which modifies secreted hedgehog, and Goat that modifies ghrelin an appetite stimulating peptide. Wnt, Hedgehog, and ghrelin require fatty acyl modification for functional activity [14]. In a parallel scenario to inhibition of Porcupine and its effects on Wnt signaling, inhibitors of Hedgehog acyltransferase block hedgehog signaling [15].

Inhibitors of Wnt signaling include small molecule Wnt antagonists, that target palmitoylation of Porcupine e.g. LGK974, or stabilize Axin e.g. Tankyrase enzyme inhibitors. Wnt signaling can also be inhibited by a CK1α activator, SSTC-104 as illustrated in figure 1 [16]. These compounds are at varying stages of preclinical and clinical evaluation. Porcupine inhibition has a more favorable specificity profile that Tankyrase enzyme inhibitors in which intestinal toxicity is a frequent toxicity. In genetically modified models Wnt inhibition through overexpression of DKK1 or TCF4 loss, can also cause gut toxicity [17-20]. Intestinal Paneth cells provide Wnt signaling to gut epithelial stem cells and Wnt is required for intestinal tissue homeostasis [21-23]. In contrast the orally bioavailable selective inhibitor of Porcupine LGK974 is not detrimental to intestinal homoeostasis despite inhibiting Wnt signaling [24]. In one study it did not have a deleterious histologic effect on Wnt-dependent tissues in a rat MMTV-Wnt1 xenograft tumor model. Ultimately, LGK974 can spare Wnt dependent tissues in mice and rats at efficacious anti-tumor dosages and may be therapeutically useful in humans.

Targeting the Frizzled receptor such as using radiolabelled monoclonal antibodies is another therapeutic approach. In a separate consideration secreted frizzled related proteins 1-5 (SFRP's 1-5) are a family of extracellular Wnt antagonists that binds to Wnt ligand or Frizzled receptors. These endogenous peptides have an anticancer role and SFRP expression is often epigenetically lost by gene promoter methylation in malignancy. Theoretically inhibition of excess Wnt signaling can be effected by restoration of SFRP expression. Histone Deacetylase (HDAC) inhibitors increase histone acetylation and increased gene expression. Epigenetic enhancement of tumor suppressor gene expression by HDAC inhibitors in synovial sarcoma is a recognized concept.

Wnt in sarcoma and synovial sarcoma

Fifty percent of human sarcomas of diverse histologic subtypes and 65% of cell lines have upregulated autocrine canonical Wnt signaling [25]. In some sarcomas Wnt antagonists such as FRP1, FRP2, FRP4, FRP5, DKK1 and DKK2 are epigenetically silenced and some sarcomas over express LRP5 and/or LRP6. Downregulation of Wnt pathway activity either in vivo or in vitro inhibits sarcoma cellular proliferation by downregulating CDC25A, a target gene of the β-catenin-TCF complex. In one study cell lines of different sarcoma

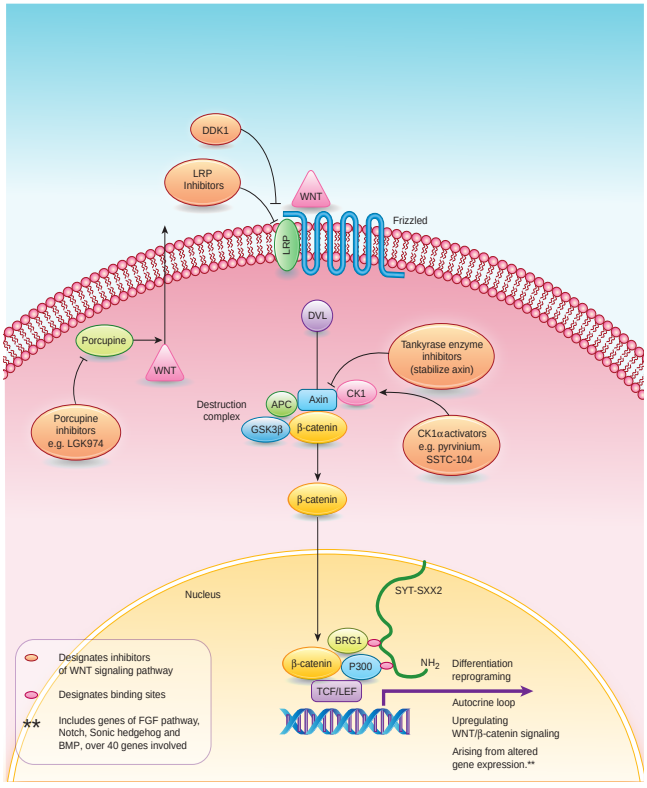

Figure 1: Pharmaceutical inhibition of the WNT signaling pathway in synovial sarcoma.

subtypes were evaluated for upregulated autocrine Wnt signaling. The assessment included two synovial sarcoma cell lines (A3243 and A2095). The A3243 cell line had increased levels of uncomplexed β-catenin and DDK1/FRP were inhibited. There was no up-regulation of uncomplexed β-catenin in the A2095 cell line. In a separate study Wnt signaling was evaluated in 57 NF-1 associated tumors (plexiform neurofibromas, dermal neurofibromas and malignant peripheral nerve sheath tumors-MPNST). Nine Wnt genes were significantly dysregulated in plexiform neurofibromas compared with dermal neurofibromas [26]. In MPNST biopsies and cell lines there was altered expression of twenty Wnt genes.

Wnt signaling is activated in synovial sarcoma and β-catenin accumulates within the nucleus in 28% - 57% of cases [27]. In a published series of 49 synovial sarcomas β-catenin gene mutations occur in 8.2% and mutations of the mutation cluster region of the APC gene also occurred in 8.2% of cases [28]. In cell cultures of synovial sarcoma, tumor xenografts and a SYT-SSX2 transgenic mouse model it was demonstrated that SYT-SSX2 directly activates the canonical Wnt/β-catenin signaling pathway. This signaling is required for synovial sarcoma growth and inhibition of Wnt signaling by co-receptor blockade and small molecule CK1α activators arrested tumor growth [29]. SSTC-104 (Stemsynergy Therapeutics Inc., U.S.) was therapeutically effective in xenograft mice models injected with human synovial sarcoma tumor cells as well as in genetic mice models of synovial sarcoma. In conclusion SYT-SSX2 expression upregulates an autocrine WNT-β-catenin loop with proliferation being the primary cellular effect of Wnt activity.

Wnt signaling is upregulated by inactivating gene mutations in other tumor types

Mutated gene products within signaling pathways other than synovial sarcoma are vicariously informative of up-regulated Wnt signaling in some tumor types. These include FAT1, NOTCH, LKB1 and RNF43. The mutational status of the relevant genes in synovial sarcoma remains poorly characterized perhaps because of low tumor prevalence. Knowledge of the effect that pathways involving the proteins arising from these genes have on Wnt signaling may be useful in designing combinatorial therapeutic approaches to optimize Wnt inhibition.

Mutational deactivation of FAT1 an associate member of the Hippo signaling pathway, promotes Wnt signaling. FAT1 deactivation occurs in glioblastoma multiforme (20.5%) as well as colorectal cancer (7.7%) and Head and Neck Squamous Cell Carcinoma (HNSCC) (6.7%) [30]. The central axis of the Hippo signaling pathway involves successive phosphorylation of MST1/2 followed by the LST1/2 tumor suppressor gene products. This leads to phosphorylation and consequent nuclear exclusion of the co-transcriptional regulator YAP (YES associated protein) with decreased cellular proliferation and apoptosis. Soft tissue sarcomas arise spontaneously in 14% of murine models with homozygous loss of *Lats1*. Furthermore 83% of *Lats1*$^{-/-}$ mice develop sarcomas secondary to carcinogenic treatment [31]. In alveolar rhabdomyosarcoma, the PAX3-FOXO1 fusion oncogene up-regulates RASSF4 [32]. This enhanced expression of RASSF4 inhibits MST1 signaling to MOB1 another associate member of the Hippo pathway causing promotion of cellular senescence, cell cycle progression and tumorigenesis. Therefore the Hippo pathway is of emergent importance in the pathogenesis of sarcoma.

Interrogating other tumors, NOTCH deactivation in HNSCC up-regulates Wnt signaling. The tumor suppressor gene product LKB1 usually restrains activity of Frizzled and *LKB1*mutations occur in 15-35%% of cases of non-small cell lung cancer and 20% of cervical cancers [14,33]. Lastly, RNF43 a trans-membrane ubiquitin ligase promotes turnover of Frizzled and is mutated in cystic pancreatic cancer [34,35].

Interacting networks in synovial sarcoma

Unsupervised gene expression analysis of 177 soft tissue sarcomas found that synovial sarcomas segregate along with other sarcoma subtypes into a cluster characterized by type specific genetic alterations [36]. Altered gene expression from developmentally important signaling pathways including FGFR, EGFR, Notch, Hedgehog, RAR, KIT and Wnt were characteristic discriminatory signatures within this group. Within synovial sarcomas in particular there were over 4000 differentially expressed genes. These included members of the FGF receptor and EGF signaling systems. Altered expression of constituent member genes of the hedgehog-signaling system such as *SMO* and *PTCH* as well as *BMP7*, *FOXM*1 and *CSNK1E* was seen. Genes within the Notch signaling system including *JAG1*, *NOTCH1* and the transducer-like enhancer of split genes also had changes in expression levels. Overexpression of the Wnt signaling pathway was identified with overexpression of *LEF1*, *AXIN2*, *TCF7*, *WISP2* and the frizzled homologues. Altered expression of genes involved in remodeling chromatin including histones and *SWI/SNF* was also seen. An analogy has been made between committed hematopoietic progenitors reverting back to a stem-cell state in hematopoietic malignancies and sarcomas, a mesenchymal stem cell/progenitor disease recapitulating different soft tissue counterparts [37].

The Wnt pathway controls lineage designation by interacting with other pathways including the FGF pathway. This is of therapeutic interest as the FGF pathway promotes the growth of synovial sarcoma cells [9]. Inferences from the work of *Barham* conclude that WNT/β-catenin in synovial sarcoma is upstream of the FGF cascade. The expression of 22 *FGF* and 4 *FGF* receptors in 18 primary synovial sarcoma tumors and 5 cell lines was determined by reverse transcriptase-PCR in one study [38]. *FGF2*, *FGF8*, *FGF9*, *FGF11*, and *FGF18* were commonly expressed. Several FGFs had growth stimulatory effects particularly FGF8 which stimulated growth in all evaluated cell lines. FGF signaling induced phosphorylation of ERK1/2 and p38MAPK. Inhibition of FGF signaling led to cell cycle arrest and growth inhibition in-vitro and in vivo in synovial sarcoma. This was accompanied by down-regulation of phosphorylated ERK1/2 and an ERK kinase inhibitor exhibited growth inhibitory effects. There was no down-regulation of p38MAPK with inhibition of FGF signaling. The other MAPK family member c-JUN is not phosphorylated by FGF signaling. Temporal and spatial embryonic co-expression of FGF8 and FGF18 is often observed [39]. FGF18 is mitogenic in colorectal carcinoma where its expression is upregulated by Wnt signaling [40]. FGF8 is often expressed in synovial sarcomas as previously mentioned. Selective inhibitors of ERK1 and ERK2 include SCH772984, an ATP-competitive inhibitor, which may merit therapeutic evaluation in synovial sarcoma. Overall the interaction between Wnt signaling and FGF signaling is the best characterized of

targetable developmental pathways in synovial sarcoma.

In another interaction of developmental pathways of interest the genes Notch1, JAG1 and the Transducing-Like Enhancer (TLE) of split genes are differentially upregulated in synovial sarcoma. These TLE genes are transcriptional regulators, Notch targets and participate in embryogenesis. They co-operate with the Wnt/β-catenin pathway in synovial sarcoma [41-43]. Overexpression of TLE1 is a discriminatory marker of synovial sarcoma and is independent of gene fusion typeor degree of differentiation [44-46].

Future molecular therapeutic strategies

The U.S. National Cancer Institute has initiated a clinical trial, targeting the developmental pathways Hedgehog and Notch in sarcoma. This is of Vismodegib and the gamma-secretase/Notch signaling pathway inhibitor RO4929097 in patients with advanced/metastatic sarcoma (NCT01154452). Adult synovial sarcoma was one of the inclusion conditions. In a separate development a phase Ia/Ib clinical trial evaluating the bio distribution, optimal recommended dose and safety of a radiolabelled monoclonal antibody that targets the Frizzled homologue 10 (SYNFRIZZ) has commenced (NCT01469975). The gene encoding frizzled homologue 10 is overexpressed in synovial sarcoma whereas it is undetectable in normal tissue except the placenta. OTSA101 is a chimeric humanized monoclonal antibody against FZD10. Yttrium 90-radiolabelled OTSA101 has significant antitumor activity but non-radiolabelled OTSA101 has only weak antagonist activity. The study population comprises patients with refractory or relapsed non-resectable synovial sarcoma.

Conclusion

The SYT-SSX2 fusion protein induces epigenetic gene (de) regulation [47]. WNT pathway activity is also aberrantly activated by SYT-SSX2. Accumulating evidence suggests that Wnt has a role in synovial sarcoma and inhibition of Porcupine is antagonistic to Wnt signaling. Early phase clinical trials of the Porcupine inhibitor, LGK974 have not commenced to date. However in future the therapeutic benefit of inhibiting Wnt signaling may be optimized by other strategies including using fibroblast growth factor receptor antagonists, which have previously been used in clinical trials for other tumor types.

References

1. Mackall CL, Meltzer PS, Helman LJ. Focus on sarcomas. See comment in PubMed Commons below Cancer Cell. 2002; 2: 175-178.
2. Naka N, Takenaka S, Araki N, Miwa T, Hashimoto N, Yoshioka K, et al. Synovial sarcoma is a stem cell malignancy. See comment in PubMed Commons below Stem Cells. 2010; 28: 1119-1131.
3. Haldar M, Hancock JD, Coffin CM, Lessnick SL, Capecchi MR. A conditional mouse model of synovial sarcoma: insights into a myogenic origin. See comment in PubMed Commons below Cancer Cell. 2007; 11: 375-388.
4. Nagayama S, Katagiri T, Tsunoda T, Hosaka T, Nakashima Y, Araki N, et al. Genome-wide analysis of gene expression in synovial sarcomas using a cDNA microarray. See comment in PubMed Commons below Cancer Res. 2002; 62: 5859-5866.
5. Sandberg A, Bridge J. Updates on the cytogenetics and molecular genetics of bone and soft tissue tumors: alveolar soft part sarcoma. See comment in PubMed Commons below Cancer Genet Cytogenet. 2002; 136: 1-9.
6. Cappello F, Barnes L. Synovial sarcoma and malignant mesothelioma of the pleura: review, differential diagnosis and possible role of apoptosis. See comment in PubMed Commons below Pathology. 2001; 33: 142-148.
7. Saito T, Oda Y, Sugimachi K, Kawaguchi K, Tamiya S, Tanaka K, et al. E-cadherin gene mutations frequently occur in synovial sarcoma as a determinant of histological features. See comment in PubMed Commons below Am J Pathol. 2001; 159: 2117-2124.
8. Garcia CB, Shaffer CM, Eid JE. Genome-wide recruitment to Polycomb-modified chromatin and activity regulation of the synovial sarcoma oncogene SYT-SSX2. See comment in PubMed Commons below BMC Genomics. 2012; 13: 189.
9. Garcia CB, Shaffer CM, Alfaro MP, Smith AL, Sun J, Zhao Z, et al. Reprogramming of mesenchymal stem cells by the synovial sarcoma-associated oncogene SYT-SSX2. See comment in PubMed Commons below Oncogene. 2012; 31: 2323-2334.
10. Polakis P. Wnt signaling in cancer. See comment in PubMed Commons below Cold Spring Harb Perspect Biol. 2012; 4.
11. Nusse R, Varmus H. Three decades of Wnts: a personal perspective on how a scientific field developed. See comment in PubMed Commons below EMBO J. 2012; 31: 2670-2684.
12. Verheyen EM, Gottardi CJ. Regulation of Wnt/beta-catenin signaling by protein kinases. See comment in PubMed Commons below Dev Dyn. 2010; 239: 34-44.
13. Herr P, Basler K. Porcupine-mediated lipidation is required for Wnt recognition by Wls. See comment in PubMed Commons below Dev Biol. 2012; 361: 392-402.
14. Lum L, Clevers H. Cell biology. The unusual case of Porcupine. See comment in PubMed Commons below Science. 2012; 337: 922-923.
15. Petrova E, Rios-Esteves J, Ouerfelli O, Glickman JF, Resh MD. Inhibitors of Hedgehog acyltransferase block Sonic Hedgehog signaling. See comment in PubMed Commons below Nat Chem Biol. 2013; 9: 247-249.
16. Yeh JR, Peterson RT. Novel Wnt antagonists target porcupine and Axin. See comment in PubMed Commons below Nat Chem Biol. 2009; 5: 74-75.
17. Chen B, Dodge ME, Tang W, Lu J, Ma Z, Fan CW, et al. Small molecule-mediated disruption of Wnt-dependent signaling in tissue regeneration and cancer. See comment in PubMed Commons below Nat Chem Biol. 2009; 5: 100-107.
18. Lau T, Chan E, Callow M, Waaler J, Boggs J, Blake RA, et al. A novel tankyrase small-molecule inhibitor suppresses APC mutation-driven colorectal tumor growth. See comment in PubMed Commons below Cancer Res. 2013; 73: 3132-3144.
19. Kuhnert F, Davis CR, Wang HT, Chu P, Lee M, Yuan J, et al. Essential requirement for Wnt signaling in proliferation of adult small intestine and colon revealed by adenoviral expression of Dickkopf-1. See comment in PubMed Commons below Proc Natl Acad Sci U S A. 2004; 101: 266-271.
20. van Es JH, Haegebarth A, Kujala P, Itzkovitz S, Koo BK, Boj SF, et al. A critical role for the Wnt effector Tcf4 in adult intestinal homeostatic self-renewal. See comment in PubMed Commons below Mol Cell Biol. 2012; 32: 1918-1927.
21. Durand A, Donahue B, Peignon G, Letourneur F, Cagnard N, Slomianny C, et al. Functional intestinal stem cells after Paneth cell ablation induced by the loss of transcription factor Math1 (Atoh1). See comment in PubMed Commons below Proc Natl Acad Sci U S A. 2012; 109: 8965-8970.
22. Kim TH, Escudero S, Shivdasani RA. Intact function of Lgr5 receptor-expressing intestinal stem cells in the absence of Paneth cells. See comment in PubMed Commons below Proc Natl Acad Sci U S A. 2012; 109: 3932-3937.
23. Sato T, van Es JH, Snippert HJ, Stange DE, Vries RG, van den Born M, et al. Paneth cells constitute the niche for Lgr5 stem cells in intestinal crypts. See comment in PubMed Commons below Nature. 2011; 469: 415-418.
24. Liu J, Pan S, Hsieh MH, Ng N, Sun F, Wang T, et al. Targeting Wnt-driven cancer through the inhibition of Porcupine by LGK974. See comment in PubMed Commons below Proc Natl Acad Sci U S A. 2013; 110: 20224-20229.

25. Vijayakumar S, Liu G, Rus IA, Yao S, Chen Y, Akiri G, et al. High-frequency canonical Wnt activation in multiple sarcoma subtypes drives proliferation through a TCFβ-catenin target gene, CDC25A. See comment in PubMed Commons below Cancer Cell. 2011; 19: 601-612.

26. Luscan A, Shackleford G, Masliah-Planchon J, Laurendeau I, Ortonne N, Varin J, et al. The activation of the WNT signaling pathway is a Hallmark in neurofibromatosis type 1 tumorigenesis. See comment in PubMed Commons below Clin Cancer Res. 2014; 20: 358-371.

27. Barretina J, Taylor BS, Banerji S, Ramos AH, Lagos-Quintana M, Decarolis PL, et al. Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. See comment in PubMed Commons below Nat Genet. 2010; 42: 715-721.

28. Saito T, Oda Y, Sakamoto A, Kawaguchi K, Tanaka K, Matsuda S, et al. APC mutations in synovial sarcoma. See comment in PubMed Commons below J Pathol. 2002; 196: 445-449.

29. Barham W, Frump AL, Sherrill TP, Garcia CB, Saito-Diaz K, VanSaun MN, et al. Targeting the Wnt pathway in synovial sarcoma models. See comment in PubMed Commons below Cancer Discov. 2013; 3: 1286-1301.

30. Morris LG, Kaufman AM, Gong Y, Ramaswami D, Walsh LA, Turcan Åž, et al. Recurrent somatic mutation of FAT1 in multiple human cancers leads to aberrant Wnt activation. See comment in PubMed Commons below Nat Genet. 2013; 45: 253-261.

31. St John MA, Tao W, Fei X, Fukumoto R, Carcangiu ML, Brownstein DG, et al. Mice deficient of Lats1 develop soft-tissue sarcomas, ovarian tumours and pituitary dysfunction. See comment in PubMed Commons below Nat Genet. 1999; 21: 182-186.

32. Crose LE, Galindo KA, Kephart JG, Chen C, Fitamant J, Bardeesy N, et al. Alveolar rhabdomyosarcoma-associated PAX3-FOXO1 promotes tumorigenesis via Hippo pathway suppression. See comment in PubMed Commons below J Clin Invest. 2014; 124: 285-296.

33. Shackelford DB, Shaw RJ. The LKB1-AMPK pathway: metabolism and growth control in tumour suppression. See comment in PubMed Commons below Nat Rev Cancer. 2009; 9: 563-575.

34. Wu J, Jiao Y, Dal Molin M, Maitra A, de Wilde RF, Wood LD, et al. Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108: 21188-21193.

35. Ding L, Getz G, Wheeler DA, Mardis ER, McLellan MD, Cibulskis K, et al. Somatic mutations affect key pathways in lung adenocarcinoma. See comment in PubMed Commons below Nature. 2008; 455: 1069-1075.

36. Francis P, Namlos HM, Muller C, Eden P, Fernebro J, Berner JM, et al. Diagnostic and prognostic gene expression signatures in 177 soft tissue sarcomas: hypoxia-induced transcription profile signifies metastatic potential. BMC genomics. 2007; 8: 73.

37. Wunder JS, Nielsen TO, Maki RG, O'Sullivan B, Alman BA. Opportunities for improving the therapeutic ratio for patients with sarcoma. See comment in PubMed Commons below Lancet Oncol. 2007; 8: 513-524.

38. Ishibe T, Nakayama T, Okamoto T, Aoyama T, Nishijo K, Shibata KR, et al. Disruption of fibroblast growth factor signal pathway inhibits the growth of synovial sarcomas: potential application of signal inhibitors to molecular target therapy. Clinical cancer research : an official journal of the American Association for Cancer Research. 2005; 11: 2702-2712.

39. Ohuchi H, Kimura S, Watamoto M, Itoh N. Involvement of fibroblast growth factor (FGF)18-FGF8 signaling in specification of left-right asymmetry and brain and limb development of the chick embryo. See comment in PubMed Commons below Mech Dev. 2000; 95: 55-66.

40. Shimokawa T, Furukawa Y, Sakai M, Li M, Miwa N, Lin YM, et al. Involvement of the FGF18 gene in colorectal carcinogenesis, as a novel downstream target of the beta-catenin/T-cell factor complex. See comment in PubMed Commons below Cancer Res. 2003; 63: 6116-6120.

41. Pretto D, Barco R, Rivera J, Neel N, Gustavson MD, Eid JE. The synovial sarcoma translocation protein SYT-SSX2 recruits beta-catenin to the nucleus and associates with it in an active complex. See comment in PubMed Commons below Oncogene. 2006; 25: 3661-3669.

42. Baird K, Davis S, Antonescu CR, Harper UL, Walker RL, Chen Y, et al. Gene expression profiling of human sarcomas: insights into sarcoma biology. See comment in PubMed Commons below Cancer Res. 2005; 65: 9226-9235.

43. Rota R, Ciarapica R, Miele L, Locatelli F. Notch signaling in pediatric soft tissue sarcomas. BMC medicine. 2012; 10: 141.

44. Segal NH, Pavlidis P, Antonescu CR, Maki RG, Noble WS, DeSantis D, et al. Classification and subtype prediction of adult soft tissue sarcoma by functional genomics. See comment in PubMed Commons below Am J Pathol. 2003; 163: 691-700.

45. Terry J, Saito T, Subramanian S, Ruttan C, Antonescu CR, Goldblum JR, et al. TLE1 as a diagnostic immunohistochemical marker for synovial sarcoma emerging from gene expression profiling studies. The American journal of surgical pathology. 2007; 31: 240-246.

46. Jagdis A, Rubin BP, Tubbs RR, Pacheco M, Nielsen TO. Prospective evaluation of TLE1 as a diagnostic immunohistochemical marker in synovial sarcoma. See comment in PubMed Commons below Am J Surg Pathol. 2009; 33: 1743-1751.

47. de Bruijn DR, Allander SV, van Dijk AH, Willemse MP, Thijssen J, van Groningen JJ, et al. The synovial-sarcoma-associated SS18-SSX2 fusion protein induces epigenetic gene (de)regulation. See comment in PubMed Commons below Cancer Res. 2006; 66: 9474-9482.

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