

BAP1 Presentation

Molecular Tumor Board Meeting

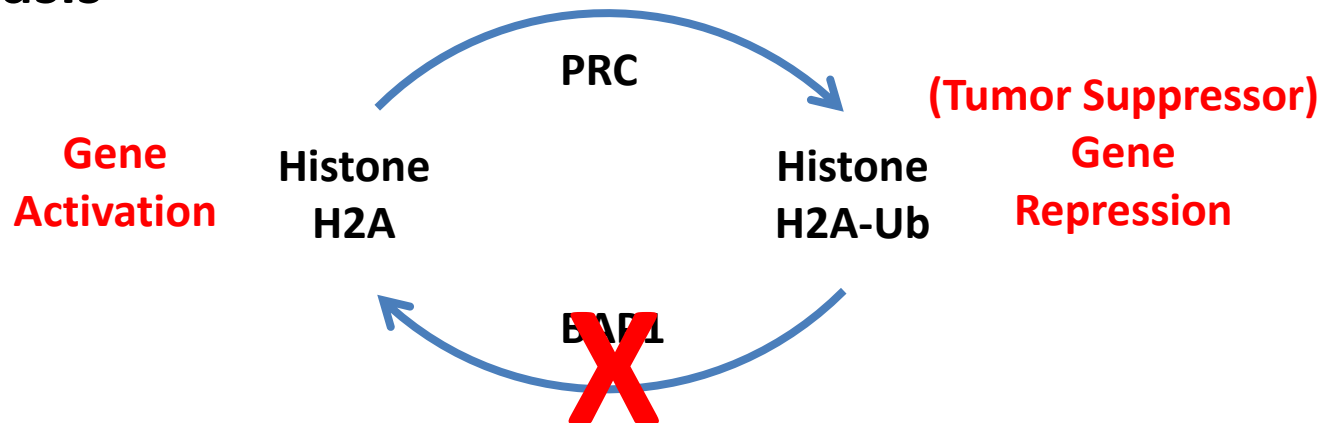
March 7, 2017

BAP1

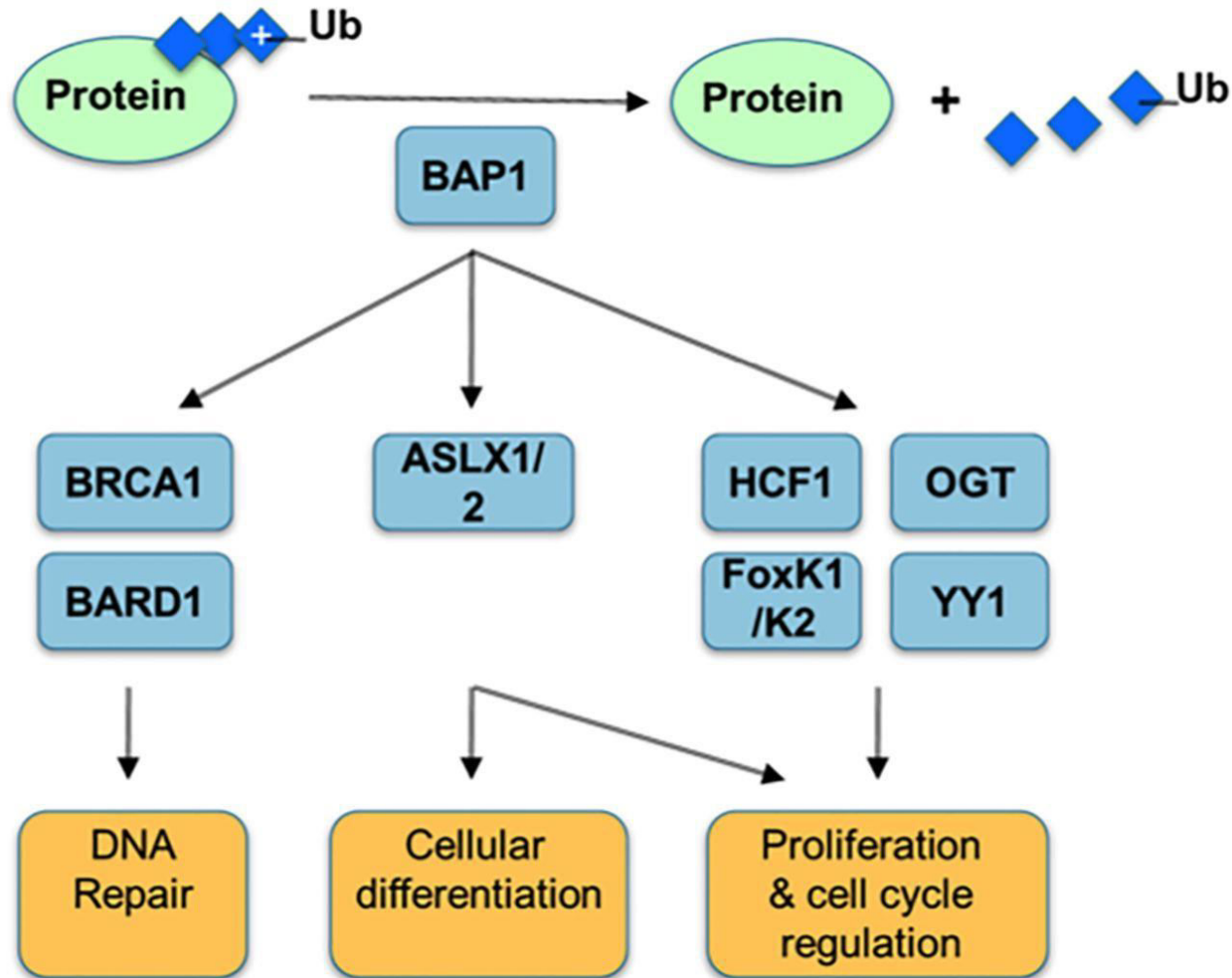
- **BAP1 = BRCA1-associated protein 1**
- **Gene Locus: chr 3p21.1**
- **90 kDa (729 aa) nuclear protein**
 - **Associates with ASXL1/2**
 - **BAP1-ASXL1/2 enzymatic activity: deubiquinating complex**
 - **polycomb group repressive deubiquitinase complex (PR-DUB)**
 - **Other protein interactions:**
 - **HCF1: Epigenetic transcriptional regulator**
 - **OGT= O-linked N-acetylglucosamine transferase**
 - **YY1: transcriptional regulator**
 - **FOXK1 and FOXK2: forkhead transcription factors**
 - **Ubiquitylated targets**
 - **HCF1**
 - **OGT**
 - **BARD1 of BRCA1/BARD1 heterodimer**
 - **Histone H2A**
 - **PGC1 α**
- **Likely physiological role: transcriptional regulator affecting cell proliferation/differentiation, gluconeogenesis, DNA damage response**
 - **BAP1 silencing changes the expression of numerous genes**

BAP1 and Polycomb Repressive Complexes

- PRC1 and PRC2 complexes repress gene expression
 - Ubiquitylate histone H2A
 - Mediate nucleosome compaction
- BRCA1/BARD1 also ubiquitylates histone H2A
- BAP1-ASXL1/2 (aka PR-DUB) deubiquitylates histone H2A
- Proper balance of histone H2A ubiquitylation by PRCs, BRCA1-BARD1, and PR-DUB may be required for cell homeostasis



Functions of BAP1 deubiquitylase

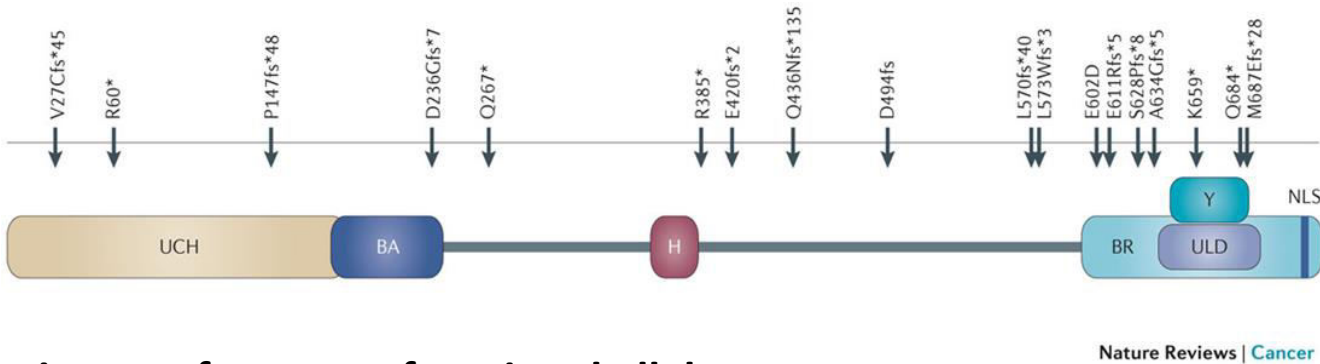


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BAP1 Mutations in Cancer

- Tumor suppressor function
- Most commonly lost in tumors by large deletions
 - Some missense, nonsense, frameshifts, and small insertions and deletions within the gene reported
- Lost/mutated in many cancer types
 - Uveal melanoma (generally highly metastatic, class 2)
 - Renal cell carcinoma
 - Generally mutually exclusive to PBRM1 mutations in RCC (36%)
 - Mesothelioma
 - High percentage (50-64%) of sporadic mesotheliomas show BAP1 loss
 - Early onset, perhaps female predominance
 - **Meningioma**
 - **High-grade rhabdoid meningiomas with BAP1 negativity (by IHC) had reduced time to recurrence compared to Bap1 positive tumors (Shankar et al. 2016)**
 - (Intrahepatic) Cholangiocarcinoma
 - Non-small cell lung cancer
 - Small cell lung cancer
 - Breast cancer
- Except for mesothelioma, BAP1 loss in cancers was associated with increased risk of recurrence and increased (all-cause and cancer-specific) mortality (Luchini et al., 2016)

BAP1 Familial Tumor Predisposition Syndrome

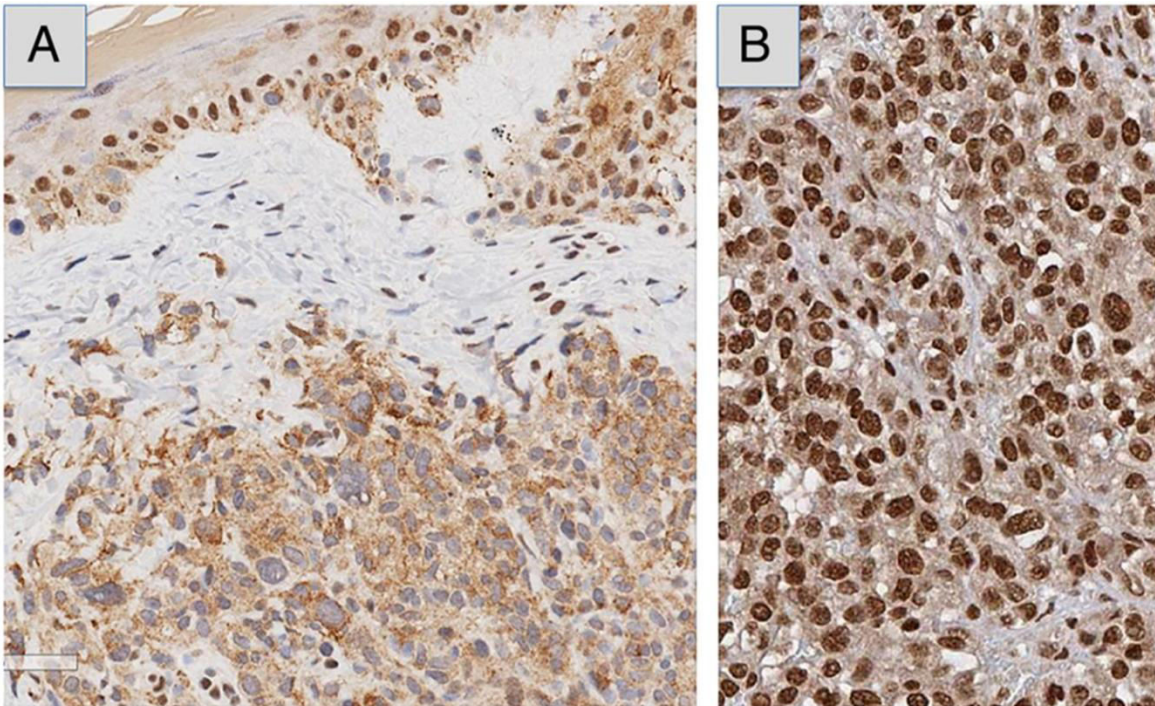


- **Inheritance of one non-functional allele**
 - Germline mutations: 73% truncating, 22% missense (predicted pathogenic)
 - Tumor predisposition in 1st and 2nd degree relatives
 - Loss/mutation of 2nd allele in cancers
- **High penetrance (up to 85%)/early onset (median age of diagnosis = 50) cancer risk**
 - *Uveal melanoma
 - Malignant mesothelioma
 - *Cutaneous melanoma
 - *Clear cell renal cell carcinoma
 - *Meningioma
 - 1972 case report of individual with meningioma, mesothelioma & uveal melanoma
 - BAP1-deficient pedigree with at least 7 affected family members showing meningioma, uveal melanoma, mesothelioma, lung cancer and others . Two patients treated for uveal melanoma developed second malignancy.
 - Other cancers with lesser frequency; multiple neoplasms common
 - atypical Spitz tumors/nevoid melanoma-like melanocytic proliferations (NEMMPs)
 - generally benign
 - ***poor prognosis**



Detection

- Other than genetic tests, BAP1 heterozygosity or loss can be assessed by immunohistochemistry



BRCA1-associated protein 1 (BAP1) immunohistochemistry. (A) Negative nuclear staining (biallelic BAP1 loss) in a cutaneous melanoma of a patient with known germline BAP1 mutation. Note: the keratinocytes with positive nuclear BAP1 staining serve as positive internal control. The keratinocytes retain one functional BAP1 allele, resulting in positive nuclear staining. (B) Another melanoma demonstrating strong nuclear BAP1 staining.

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Targeted therapies?

- **Histone deacetylase inhibitors**
 - Reversed effects of increased histone H2A ubiquitylation in BAP1-deficient uveal melanoma tumor cells; also reduced growth of UM xenografts (Landreville et al. 2012)
 - In a Phase I trial, four (30%) of 13 patients with malignant pleural mesothelioma that received vorinostat had a stabilization of their disease lasting more than 4 months; in addition, two unconfirmed partial responses were observed (Kelly et al. 2005). However, in a recently completed Phase III trial (VANTAGE 014) including 660 pre-treated advanced MPM patients, vorinostat given as a second-line or third-line therapy did not improve overall survival. Therefore, was not recommended as a therapy in malignant pleural mesothelioma patients (Krug et al 2015). Another small phase II trial (conducted on thirteen patients) with the HDAC inhibitor, belinostat, also produced negative results (Ramalingam et al. 2009). **Unclear how many of these had BAP1 mutations.**
- **PRC2 inhibition**
 - PRC2 subunits EZH2 and EED are often overexpressed in mesothelioma
 - PRC2 may be upregulated in BAP1-deficient tumors
- **Ionizing Radiation or PARP1 inhibition**
 - High genome instability in BAP1-deficient renal cell carcinoma may reflect associated mitotic spindle or DNA repair defect
 - Silencing of BAP1 in HeLa cells resulted in defects in the DNA damage response and hypersensitivity to ionizing radiation
- In cholangiocarcinoma cell lines with differential BAP1 expression, sensitivity to gemcitabine was greater in low BAP1 expressing or BAP1 knockout cells compared with high BAP1 expressing cells or control haplo-insufficient cells. Similar results were observed with TSA (HDAC inhibitor), olaparib (PARP inhibitor), b-AP15 (Ub-specific processing protease inhibitor) but not with GSK126, which inhibits PRC2. A differential synergistic effect was observed in combinations of gemcitabine with olaparib or GSK126 in low BAP1-expressing cells and TSA or bAP15 in high BAP1-expressing cells, indicating BAP1 dependent target-specific synergism and sensitivity to gemcitabine. NEAT1 lncRNA was upregulated upon loss of BAP1; NEAT-1 levels impact chemosensitivity. (Parasramka et al., 2017)

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