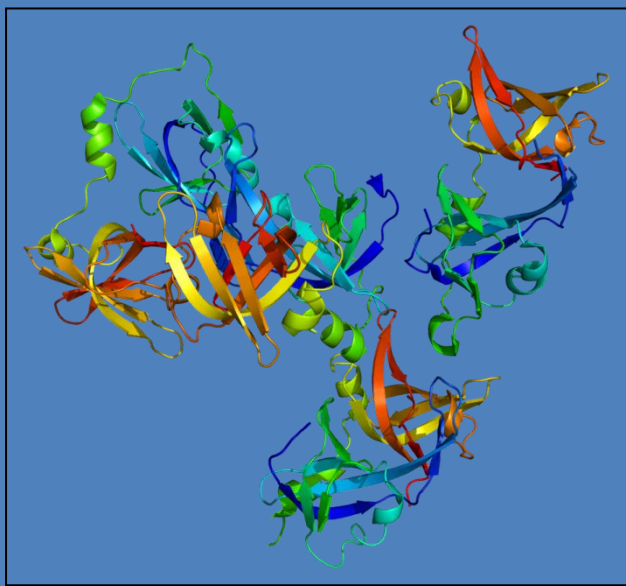




Association between IFI16 and BRCA1 during ovarian carcinogenesis

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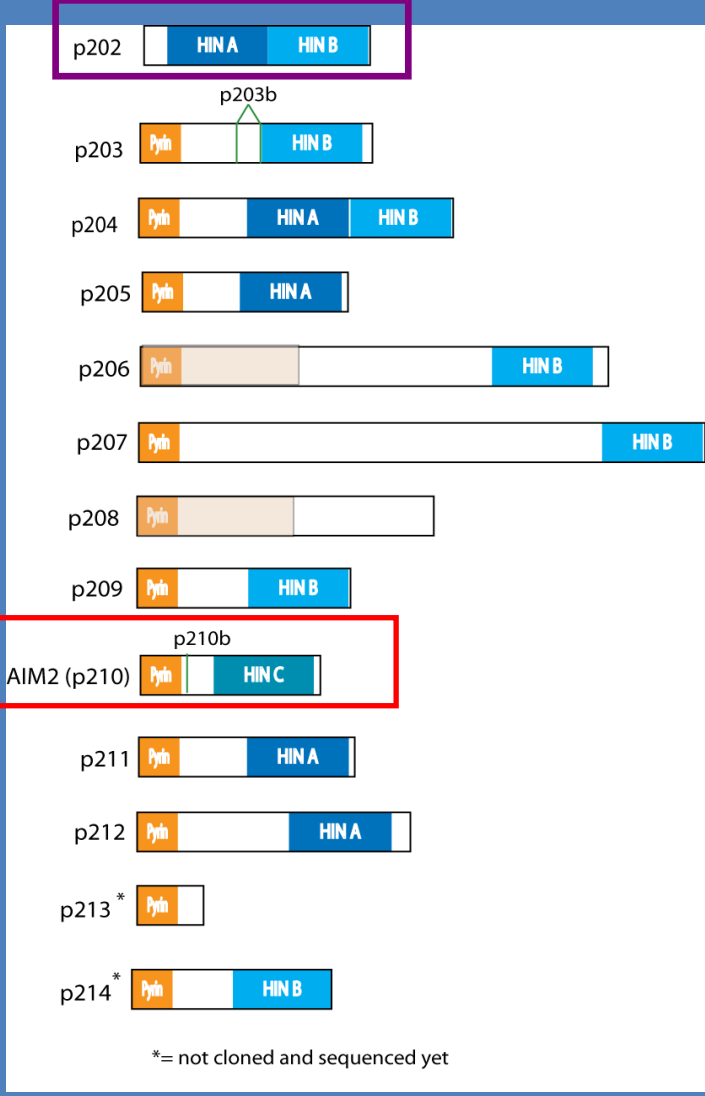
Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich, United Kingdom



HIN-200 FAMILY PROTEINS

Mouse

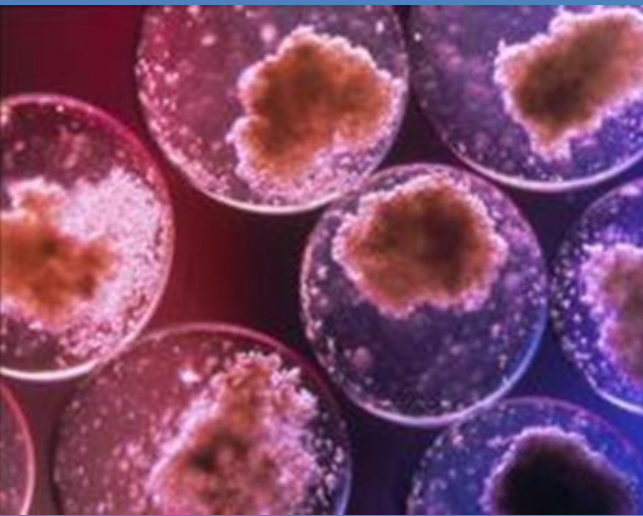
Human



- Interferon inducible
 - 200 amino acid HIN domains
 - Pyrin domains
- Modified from Gariglio et al., J IFN Cyt Res 2011*

BRCA1/IFI16

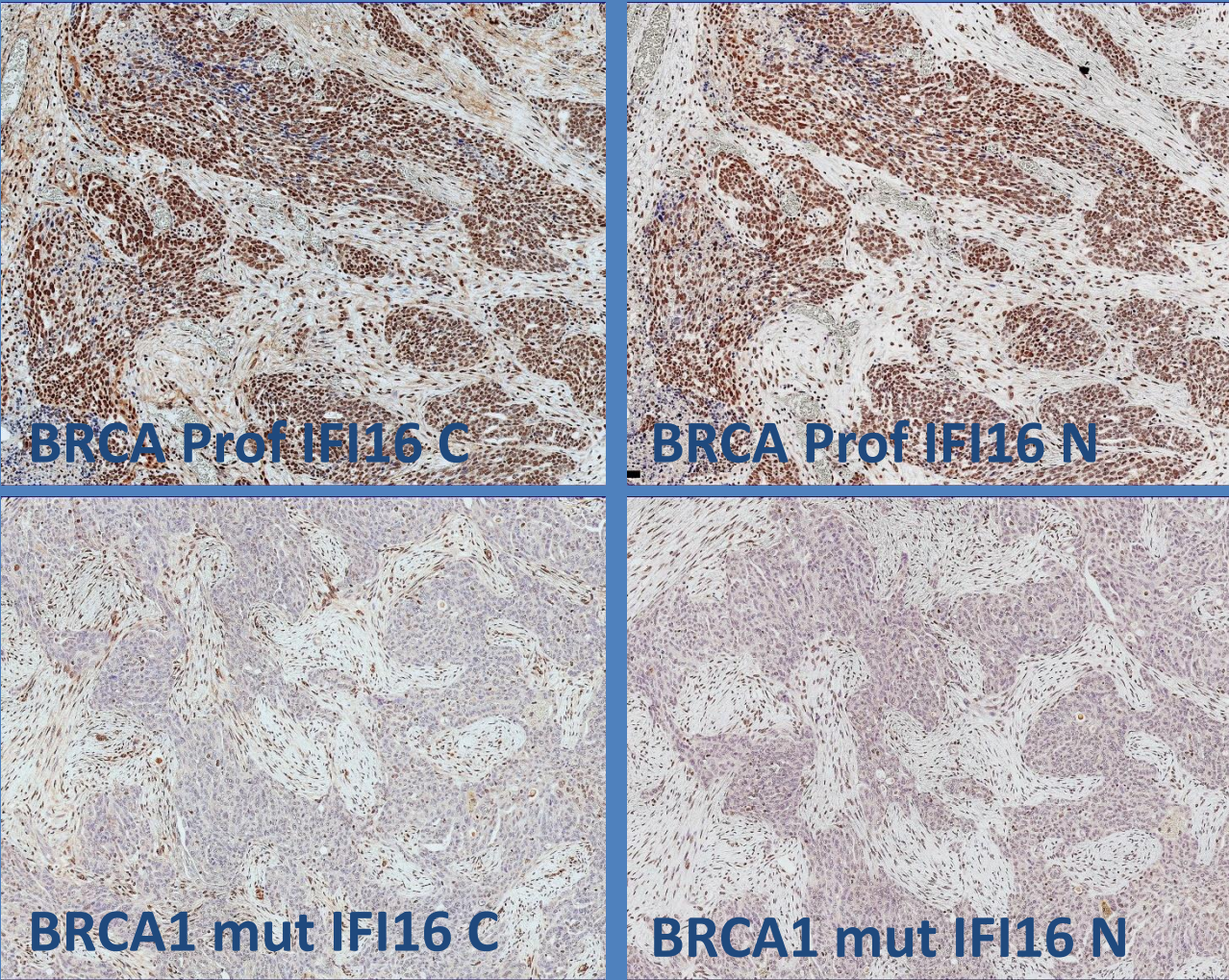
- *Aglipay et al.* identified IFI16 as a previously unknown member to the set of BRCA1-interacting proteins
- The Pyrin domain of IFI16 is a protein–protein interaction module that is important for binding to BRCA1
- BRCA1/IFI16 complex is involved in the p53-mediated cell death pathway.



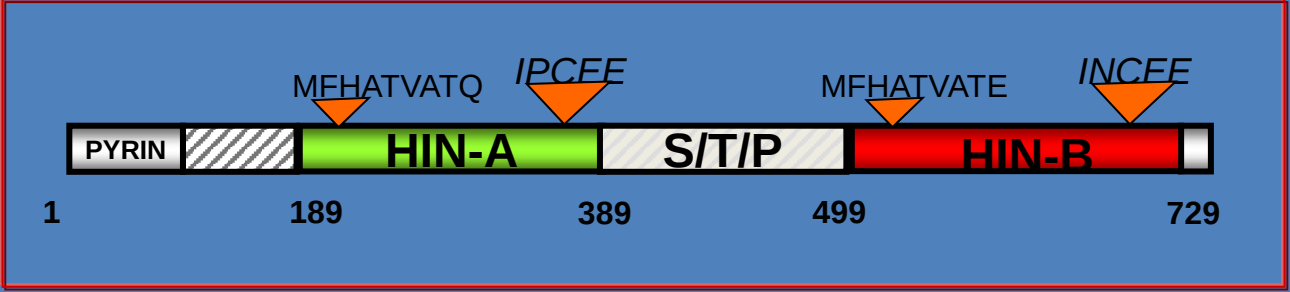
Nucleolar accumulation of IFI16 was restored by re-expression of wild-type BRCA1 in BRCA1-mutated cells, strongly suggesting that IFI16 is involved in the BRCA1 pathway activated by DNA damage

Aglipay et al. Oncogene 2003

IFI16 EXPRESSION IN BRCA PROFICIENT AND BRCA1 MUTATED OVARIAN CARCINOMA



INTERFERON INDUCIBLE IFI16 GENE



- Member of the IFN-inducible **p200** (PYHIN) family proteins
- Two copies of the 200 aa **HIN** domain (type a and b) → low-affinity DNA binding activity
- Conserved peptide motifs (e.g. **MFHATVAT** or **IXCXE**) → interaction with different transcription factors (e.g. p53)
- **PAAD/DAPIN/PYRIN** domain (N-terminus) → involved in apoptotic and inflammatory pathways

MATERIALS AND METHODS

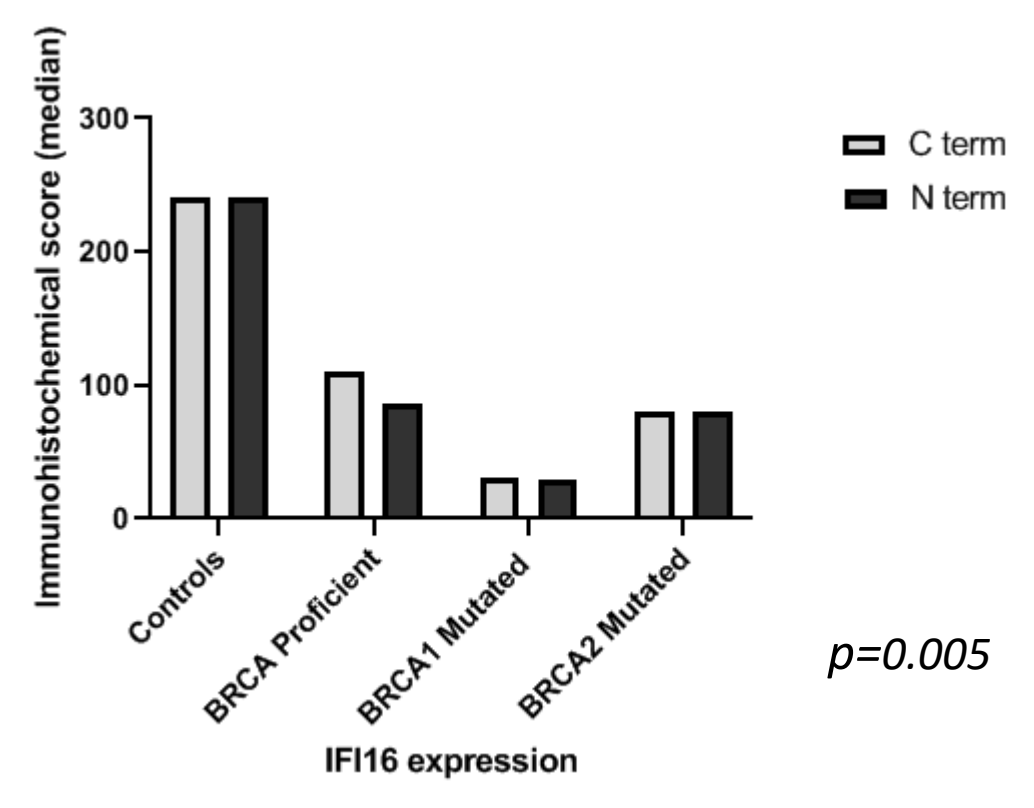
Sections derived from pathology samples containing tissue of ovarian carcinoma were sent for somatic BRCA1/2 mutation testing. Germline testing was performed on blood samples.

The patients' tumour DNA sample was screened for mutations by Next Generation Sequencing (NGS) analysis. The immunohistochemical assessment of IFI16 C terminus and N terminus antibody was performed on the same specimens and normal tubal tissue used as control. The results obtained were compared to the immunohistochemical expression of ER, p53 and MMR proteins.

RESULTS

BRCA testing: total 37 specimens
 3 insufficient material
 4 BRCA1 mutated
 3 BRCA2 mutated

IFI16 EXPRESSION IN BRCA PROFICIENT AND BRCA1 MUTATED OVARIAN CARCINOMA

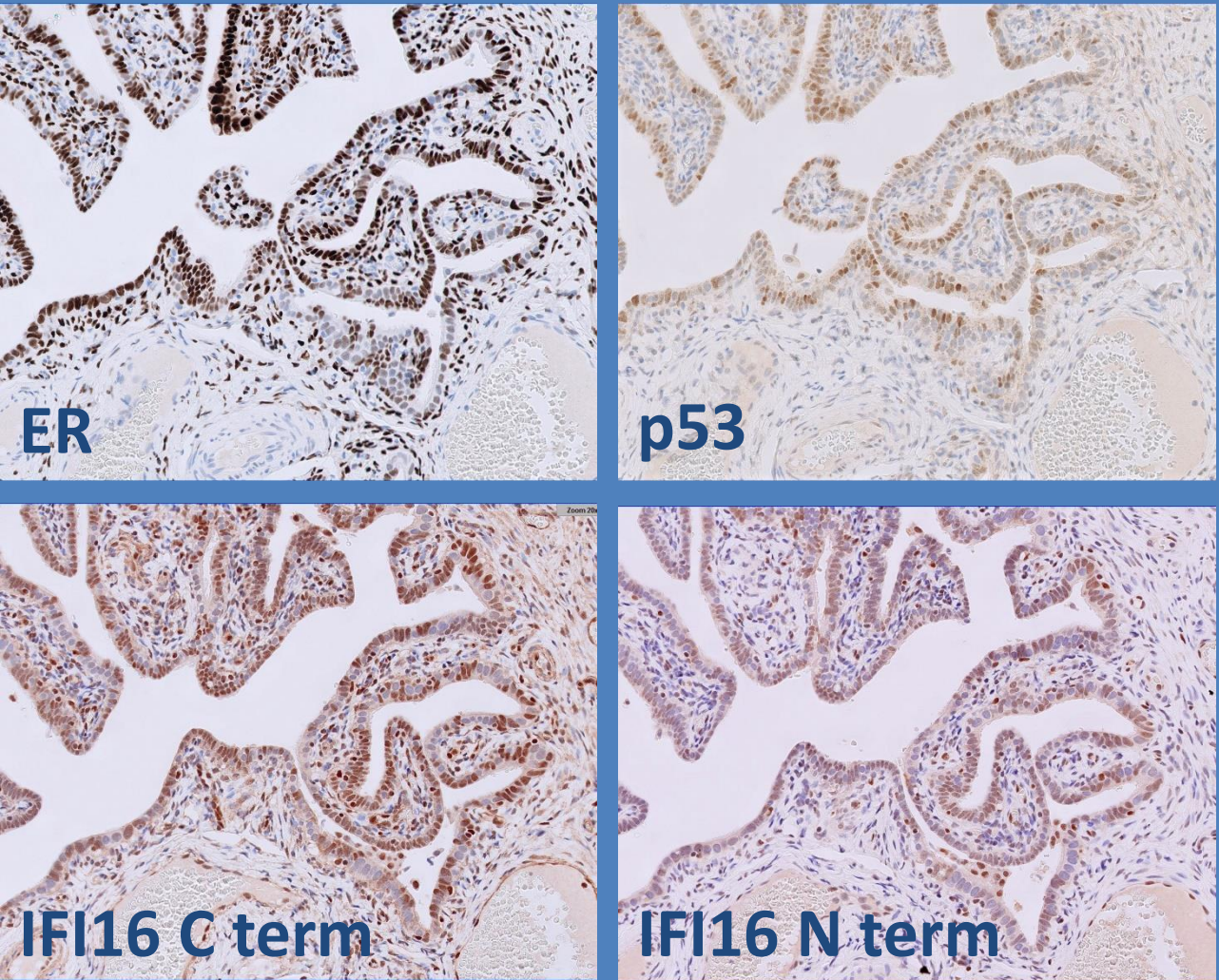


THE MULTIFACETED ACTIVITY OF IFI16

- Suppression of cell proliferation by blocking G1/S transition
- Regulation of cell differentiation
- Senescence induction by hTERT down-regulation
- Apoptosis induction by caspase-2 and caspase-3 activation
- Induction of inflammation through activation of pro-inflammatory molecules
- Innate immune sensor for intracellular DNA

Unterholzner L et al., Nature Immunology 2010;
Kerur N et al., Cell Host Microb 2011

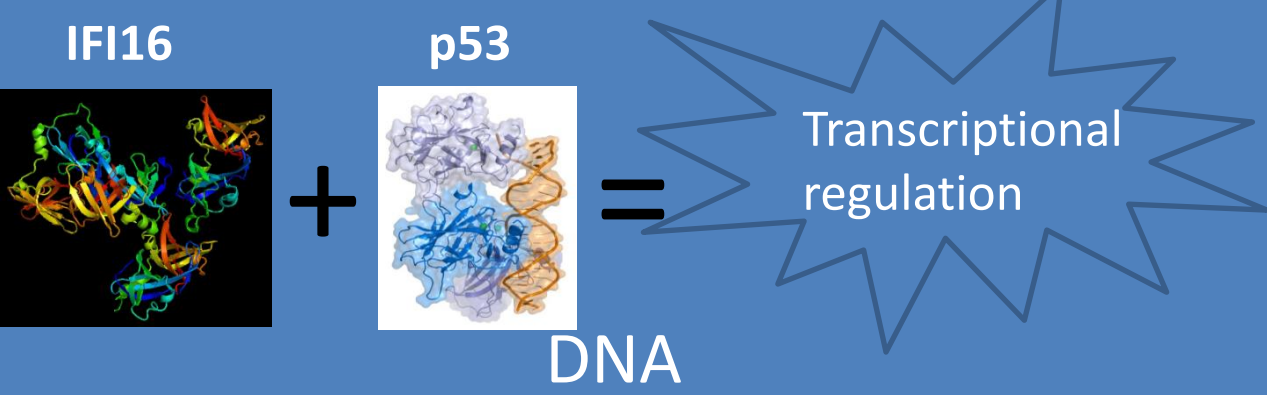
IFI16 EXPRESSION IN FALLOPIAN TUBE EPITHELIUM



CONCLUSIONS

- IFI16 is normally express in tubal epithelium in a pattern that overlaps with ER and p53 expression
- IFI16 expression in ovarian serous carcinoma is dependent on proficient BRCA 1 gene
- BRCA1 mutated ovarian carcinomas show significant decrease in expression of IFI16 in comparison to BRCA1 proficient tumours
- There is a significant variability in IFI16 expression within BRCA proficient tumours
- No correlation is identified between ER, p53 and IFI16 expression in ovarian carcinoma tissues (data not shown)
- One of BRCA1 mutated tumours showed aberrant immunohistochemical expression of MLH1, MSH6 and PMS2

BINDS TO C-TERMINAL REGION OF P53



All the proteins of the HIN200 family have a highly conserved region rich in leucines at the N-terminus capable of binding DNA, the presence of which indicates a possible transcriptional activity

Contact

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