PROFERRED PAPER SESSION

SARCOMA

Abstracts no. 3580, 3590, 3600

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Chemo–responsiveness predictive biomarker discovery for osteosarcoma using microRNA–microarray

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miRNAs

- MicroRNAs (miRNAs) are single-stranded noncoding RNAs involved in various biological processes through post-transcriptional modifications.

- There are known to be at least 4000 miRNAs in human genome.

- Regulate approx 50% of human genes. Each miRNA likely controls hundreds of gene transcripts.

- Can have an oncogenic (overexpressed) or tumour suppressive role (underexpressed), hence their interest as a biomarker.
miRNAs in Osteosarcoma

Work flow

4 Responders

miRNA-microarray
(Agilent Technology, n=851)

Validation Study
• 20 samples (FFPE)
• qRT-PCR analysis
• Statistical analysis

4 Non-responders

Functional Study
• miRNA target
• Cytotoxicity
• Cell Proliferation
• Apoptosis

Large-scale validation study

Novel biomarker

- Identify potential miRNAs based on chemo response
- Validation
- Functional Study
- Large scale validation
Functional study
Cytotoxicity

- Osteosarcoma cell line (MNNG/HOS, 143B, and MG63)
- The IC$_{50}$ values were inspected before and after transfection of miR–125b and miR–100.
- Over expression of miRNAs resulted increasing drug resistance for MTX/DOX/CDDP.
miRNAtarget

- miRNA targets database

TargetScanHuman
Prediction of microRNA targets
Release 6.0: November 2011

miRBase

- miR-125b: P53, BCL-2 Family
  - Bak1 (apoptosis)
  - TP53 (apoptosis)
  - PUMA (apoptosis)

- miR-100: Rb Family
  - CTDSPL (cell cycle)
Conclusion and Next Steps

- We identified the miRNAs as predictive biomarker of chemo–response in osteosarcoma.
- miR–125b and miR–100 were up–regulated in non–responders.
- Cytotoxicity assay suggested these miRNAs may contribute to a broad spectrum of chemo–resistance mechanism.
- miR–125b and miR–100 targeted p53 and Rb pathway. These miRNAs may promote cell proliferation, and inhibit drug–induced apoptosis.
- ROC curve analysis revealed the high predictive ability of these miRNAs.

Future Studies
- Prospective validation in large clinical trials
- Role in modifying response to all 3 agents
- Other measures of miRNAs eg circulating levels

Further miRNAs identified in OS
- May have role as a Predictive Biomarker
- Single vs multiple miRNAs?
- Identified through functional screens, and then validated clinically and preclinically
A Whole Genome Approach to Better Understand the Link Between Kaposi’s Sarcoma-Associated Herpesvirus and Human Cancers

Abstract 3590

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Overview

KSHV Infected Cells:

Whole genome approach to explore genes affected by hypoxia
Hypoxia drastically changes expression profile of KSHV-infected cells.

KSHV infection induces miR-210, a key hypoxia-regulated miRNA involved in cancer.

However, viral miRNAs don’t change in response to hypoxia.
miRNA-210

- miR-210 targets and their biological functions:
  - miR-210 induces cell survival and increases cell proliferation
  - miR-210 induces angiogenesis
  - miR-210 represses mitochondrial metabolism
  - miR-210 stalls DNA repair

miR-210: the Master Hypoxamir, Chan et al. 2011
Conclusions Abstracts 3580 and 3590

• Potential value in using miRNAs to better understand the complexities of tumorigenesis

• Explore Utility of miRNAs as both a biomarker (predictive and prognostic) and in understanding pathogenic links to disease

• Potential value as a circulating biomarker

• Challenges will be in understanding their context and functional significance in individual tumour types
Clinicopathological and functional analyses of protein phosphatase 2, regulatory subunit A, alpha mutations in gastrointestinal stromal tumors

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Abstract 3600
Overview

• Mutations in \textit{PPP2R1A} only recently described (2007)
  – Most commonly reported in Ovarian and Uterine Ca
  – Only 169 cases in Cosmic database
  – Reports in other tumours, eg. prostate

• Aimed to explore PPP2R1A in GIST
  – 94 Patients
  – All primary tumours, i.e. pre-treatment
  – Why?
• 17 (18.1%) of 94 GIST cases harbored PPP2R1A mutations.

• Not isolated to WT patients

• Univariate analysis: Correlated with tumour grade/aggressiveness, and overall outcomes

• Multivariate analysis with larger numbers would be very useful
RESULTS: Functional Significance

- Limited data in gynae cancer models suggesting function through AKT
- Transduced GIST cell lines
  - Unsure how extensive their phospo-protein analysis was
Conclusions and Next Steps

• Novel and very interesting study

• Co-existing mutations in reasonable percentage of GIST cases, co-existing with other key drivers

• Value in
  • Better understanding the utility of PPP2R1A as a biomarker
  • Exploring patient cohorts post-TKI therapy
  • Understanding functional effects in more detail
  • Exploring mechanisms to target these changes