Production of fibronectin sensitizes EGFR-TKI resistant lung cancers to silver nanoparticle induced endoplasmic reticulum stress

Monica Rohde1, Christina M. Snyder1, Reetta Holmila2, Cale Fahrenholtz1, John Sloop3, George L. Donati3, Cristina M. Furdui3, Ravi Singh1, 4

Abstract

Lung cancer is the leading cause of cancer related deaths worldwide and second commonly diagnosed cancer among men and women. Epidermal growth factor receptor (EGFR) is frequently dysregulated in lung cancers and has been implicated in pathogenesis of this disease. Because of this, EGFR-tyrosine kinase inhibitors (TKIs) have since been developed as a primary form of treatment. However, many patients do not initially respond, or they inevitably develop resistance to EGFR-TKIs within 12-14 months of treatment. Therefore, discovering new drugs for these patients is increasingly important. We found that silver nanoparticles (AgNPs) are effective for the treatment of inherent and acquired resistance to EGFR-TKI in lung cancer cells. We establish that doses of AgNPs that are highly cytotoxic to EGFR-TKI resistant lung cancers are non-toxic to non-malignant lung cells. No differences were observed in the internalization or intracellular trafficking of AgNPs in AgNP sensitive cells and AgNP resistant cells, indicating that the difference in sensitivity was not due to the quantity of AgNPs internalized. Therefore, we performed mechanistic studies to identify the underlying biology of the cells that was responsible for this difference. We observed that AgNPs induce lipid peroxidation, protein oxidation and aggregation in EGFR-TKI resistant lung cancers. This then leads to irreparable endoplasmic reticulum (ER) stress, resulting in cell death. In contrast, doses of AgNPs that were lethal to EGFR-TKI resistant cancers had no effect on EGFR-TKI sensitive lung cancers. We further establish that EGFR-TKI resistant lung cancers exhibit increased expression of extracellular matrix proteins including fibronectin and collagen. Knockdown of fibronectin in EGFR-TKI resistant cells decreases their sensitivity to AgNPs by reducing baseline endoplasmic reticulum stress. This work provides a rationale for the development of AgNPs for the treatment of EGFR-TKI resistant lung cancer.

Results

Figure 1. Silver nanoparticles are more selective than gefitinib, RSL3 or erlotinib for EGFR-TKI resistant lung cancers, and increased sensitivity is not due to differences in uptake or trafficking. For all studies, non-malignant cells are shown in black, EGFR-TKI resistant cancers are shown in red, and EGFR-TKI sensitive cancers are shown in blue. (A) TGF-β restored sensitivity of all cancers to gefitinib, erlotinib and RSL3. (B) ER stress was measured by WEHI assay. (C) Uptake of 25 nM A549 was observed to be equivalent in all conditions. Localization of AgNPs was imaged by SEM, showing AgNPs were internalized by cells incubated for 5 hours to allow uptake and trafficking. AgNPs primarily localized to endosomes in both (F) PC9 and (C) CALU1 cells.

Figure 2. Silver nanoparticles induce lipid oxidation, protein oxidation, and protein aggregation in EGFR-TKI resistant lung cancer cell lines. (A) Protein aggregation in EGFR-TKI resistant cancers shown in red, and EGFR-TKI sensitive cancers are shown in black. (B) Blue To assess lipid peroxidation, cells were treated with AgNPs for 24 hours without silver and fluorescence was measured using flow cytometry. (C) Flow cytometry. (D) Cells were treated with AgNPs for 24 hr, stained with DCF-DA, and measured using flow cytometry.

Figure 3. Silver nanoparticles induce irreversible endoplasmic reticulum stress in EGFR-TKI resistant lung cancers. For all studies, EGFR-TKI resistant cancers are shown in red, and EGFR-TKI sensitive cancers are shown in blue. (A) Inhibition of fibronectin expression in RNAi obtained from the CCLE were plotted for lung cancer cell lines used in this study. (B) TNF-α was knocked down in SKLU1 cells using RNAi targeting with shRNA and verified by western blot. (C) Cells were exposed to AgNPs for 72 hrs and viability was measured by MTT assay. (D) Cells were treated with 10, 25, 37, 50, 75, 100 μg/mL AgNPs or untreated and viability was measured by flow cytometry.

Figure 4. Silver nanoparticles induce irreversible endoplasmic reticulum stress in EGFR-TKI resistant lung cancers. For all studies, EGFR-TKI resistant cancers are shown in red, and EGFR-TKI sensitive cancers are shown in blue. (A) Inhibition of fibronectin expression in RNAi obtained from the CCLE were plotted for lung cancer cell lines used in this study. (B) DCP1α was knocked down in CALU1 cells using RNAi targeting with shRNA and verified by western blot. (C) Cells were exposed to AgNPs for 72 hrs and viability was measured by MTT assay. (D) Cells were treated with 10, 25, 37, 50, 75, 100 μg/mL AgNPs or untreated and viability was measured by flow cytometry.

Conclusions

- Silver nanoparticles are toxic to EGFR-TKI resistant lung cancers at doses that are non-toxic to non-malignant cells
- Silver nanoparticles induce lipid and protein oxidation, protein aggregation, and irreversible endoplasmic reticulum stress in EGFR-TKI resistant lung cancers
- Increased secretory load of EGFR-TKI resistant lung cancers leads to their susceptibility to silver nanoparticle treatment

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Identification of Molecular Signatures Predictive of Sensitivity of Breast Cancer Cells to Silver Nanoparticles

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Abstract

Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer with high mortality that accounts for 15-20% of all breast cancer diagnoses. Patients experience high rates of relapse and metastasis. Molecular profiling shows that TNBC tumors can be classified into subtypes that differ in expression of epithelial and mesenchymal markers as well as in response to chemotherapy. TNBC cells enriched in mesenchymal markers are radiation and chemotherapy resistant, and may contribute to therapeutic resistance and tumor relapse. We previously discovered that silver nanoparticles (AgNPs) are cytotoxic to TNBCs at doses that have no effect on non-cancerous cells. Our current studies show that TNBCs expressing mesenchymal markers (VIM) are significantly more sensitive to AgNPs than TNBCs that express epithelial markers (CDH1). Furthermore, lung, prostate, colorectal, and ovarian cancers that express mesenchymal markers are more sensitive to AgNPs than cancers of the same origin that express epithelial markers. This shared vulnerability of mesenchymal cancers to AgNPs indicates that there is an underlying biology that is responsible for this. We performed mechanistic studies to determine the cause of these differences. Our results show that AgNPs induce protein aggregation, endoplasmic reticulum stress, and lipid peroxidation in TNBCs expressing a mesenchymal phenotype, but not in epithelial TNBCs. We further identify elevated synthesis of extracellular matrix (ECM) proteins including fibronectin and collagen, as well as high expression of long-chain-fatty-acid CoA ligase 4 (ACSL4), as being distinguishing features of AgNP sensitive cancers. The burden of synthesis of ECM proteins increases sensitivity of cells to ER stress, and ACSL4 is essential for incorporating oxidizable lipids into cell membranes. By detailing these mechanisms of action and identifying genetic signatures associated with sensitivity to AgNPs, our results highlight shared vulnerabilities of mesenchymal cancer cell populations, which may be exploited by AgNPs or other therapies.

Results

Figure 1. Mesenchymal markers, EMT, and protein synthesis in cells treated with AgNP. mRNA expression data for ECM and CDH1 were obtained from the Cancer Cell Line Encyclopedia (CCLE) and expressed as reads per million (RPKM). GAPDH was used as a housekeeping gene. Relative mRNA expression was quantified by qRT-PCR and used to calculate fold change (FC) for each cell line. Statistical analysis was performed by two-way ANOVA and post-hoc Tukey’s test. Significance differences between mesenchymal (red) and epithelial (blue) cancer lines are indicated (**p<0.01, ***p<0.001).

Figure 2. AgNPs induce lipid peroxidation, proteasomal stress, and immediate-early protein expression in mesenchymal but not epithelial TNBCs. To assess lipid peroxidation, breast cancer cells were treated with AgNPs for 24 hrs, stained with Lipofluor and fluorescence measured using confocal microscopy and flow cytometry. AgNP treated and control cells were treated with 0.125, 0.25, 50, and 100 μg/mL AgNPs for 24 h.

Figure 3. High expression of ECM proteins and ACSL4 are distinguishing features of AgNP sensitive cancer. FN1 and ACSL4 protein expression was determined by western blot. mRNA expression data was obtained from the CCLE for ECM and large secreted proteins upregulated in AgNP treated compared to AgNP sensitive breast cancer cell lines.

Key Points

- Triple negative breast (TNBC), lung, ovarian, colorectal, and prostate cancers that express mesenchymal markers are highly sensitive to AgNPs.
- AgNPs induce lipid and proteotoxic stress in mesenchymal but not epithelial TNBCs. This is characterized by lipid and protein oxidation, protein aggregation, and immediate ER stress.
- Increased synthesis of extracellular matrix (ECM) proteins such as fibronectin and collagens and ACSL4 proteins are distinguishing features of AgNP-sensitive cancers. Synthesizing large amounts of ECM proteins sensitizes cells to ER stress induced by AgNPs, and ACSL4 is essential for incorporating oxidizable lipids into cell membranes.

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Automated Tip Conditioning for Scanning Tunneling Spectroscopy

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Abstract

We apply machine-learning models trained with archived gold dI/dV spectra to analyze spectra collected during tip conditioning, so the program can stop when the tip is in a good shape for STS measurements. We manually labeled archived spectra based on their quality and resemblance to standard dI/dV spectra for gold.

Evaluating Tip Condition from dI/dV Spectra using Machine Learning Models

### Evaluating Tip Condition from dI/dV Spectra using Machine Learning Models

Figure 2. Example STS curves with different grades.

| Model            | Precision (On test set) | Recall (On test set) | ROC Area Under Curve |
|------------------|-------------------------|----------------------|----------------------|
| SGD              | 0.595                   | 0.547                | 0.807                |
| SVM              | 0.685                   | 0.733                | N/A                  |
| Decision Tree    | 0.746                   | 0.616                | 0.790                |
| Random Forest    | 0.825                   | 0.605                | 0.828                |
| AdaBoost         | 0.829                   | 0.674                | 0.942                |
| CatBoost         | 0.842                   | 0.744                | 0.943                |
| MLP              | 0.792                   | 0.663                | 0.940                |
| CNN              | 0.806                   | 0.674                | 0.935                |

Table 1. Number of dI/dV spectra with different grade.

| Grade | Number | Training Label (Are Surface States?) | dI/dV (V) |
|-------|--------|-------------------------------------|-----------|
| 1     | 285    | False                               | -0.75     |
| 2     | 250    | False                               | -0.75     |
| 3     | 210    | False                               | -0.75     |
| 4     | 160    | True                                | -0.75     |
| Total | 1000   |                                     |           |

Figure 4. Sample dI/dV spectra in the test set that are classified as (a) false positives (labeled as False, predicted as True) and (b) false negatives (labeled as True, predicted as False) by an Adaboost model.

We can see that decision tree based ensemble and boosting models and deep neural networks (MLP, CNN) have similar classification results and outperform basic models.

The performance of machine learning models listed in Table 2 does not look appealing judged just by the precision and recall scores. However, this can be due to the inconsistency of manual labeling since there is no hard criteria for grading the dI/dV spectra. The differences between spectra with different grades are minor, especially for spectra that are graded as 1 or 2. Therefore, ambiguity in manual classification introduces significant noises into the dataset labeling. The lack of good spectra for training is another reason for the compromised performances. Deep neural networks tend to overfit our sample despite the simple architectures (see supporting information) we used. Furthermore, for the machine learning models to work we have to group spectra with grade 2, 3, and 4 together and label them as good. Therefore, some poor-quality spectra with visible gold surface state might have been labeled as grade 2 and used as good spectra for training. Examples of mispredicted spectra are presented in Figure 4.

Summary and Prospects

We present an automated tip conditioning program for STS measurements based on Python and machine learning. We developed a straightforward algorithm to process and analyze topographic STM images in order to find possible tip conditioning positions on clean or sparsely covered gold surfaces. Machine learning models are used to analyze STS spectra and determine the quality of the tip. Decision tree based ensemble and boosting models and deep neural networks have similar performances on identifying usable tips with clear gold surface state and an Adaboost model is used as default for the program to be robust, adaptable, and fast. Data augmentation methods are being investigated to improve the performance of machine learning models. We expect that our program can make efficient use of the idle time of the STM (e.g., during the night) and greatly reduce the amount of research time wasted on tip conditioning for STS measurements. In the future, we expect to embed reinforcement learning into our program so that the program may be able to figure out the best poking protocol for tip conditioning.

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**Atomic scale observations of electrocatalytic process on porphyrin-modified Au(111) electrode**

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**Abstract**

The electrocatalytic performance for oxygen evolution reaction (OER) is fundamental for solar water splitting and fuel cell technologies. In this work, we report on a detailed atomic scale understanding of the electrocatalytic process on porphyrin-modified Au(111) electrode for OER. *Schematic of EC-STM* shows the methodological aspects of our analysis. *Unique domains of porphyrin networks in octanoic acid* illustrates the unique domain structures formed by porphyrin molecules in the presence of octanoic acid. *Time-dependent surface restructuring of porphyrins* highlights the dynamic changes in the surface structure over time. *In situ EC-STM measurement of Au(111) in 0.1 M NaOH* demonstrates the electrochemical behavior of Au(111) electrode in alkaline solution. *Conclusion* summarizes the main findings and their implications.

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**Introduction of metalloporphyrins and surface science**

- Electrochemical water splitting is one of the promising ways to produce hydrogen and oxygen for clean and renewable energy.
- Metalloporphyrin can be the best model system for a metal-organic catalyst to overcome the slow kinetics of OER and ORR.
- Electrochemical surface analysis is actively used to survey the enhanced electrocatalyst for potential application in solar-driven water splitting devices.
- EC-STM provides direct observation of the surface at the molecular scale at solid/liquid interface, broadening our fundamental comprehension for OER and ORR mechanism.

**Sample preparation and tip coating**

- **Au(111)/Mica** Flame annealed Au(111)/Mica Pasteur pipette Drop the droplet Immersion
- **Hexagonal-OEP** Butane gas Flame annealing for 1 min Mini desiccator in out Pyrex® petri dish Rinsing thoroughly with ultrapure water (>18.5 MQ)
- **Tip coating** Tip apex Immersion in 100 µm porphyrin/benzene Aplezon wax

**Porphyrin/Au(111) in DI water**

- **MnTPP-Au(111)**
  - MnTPP-Au(111) 1.5 nm 4 min
  - (Vtip = +0.3 V, t = +0.30 nA, E = NS V)
  - The highly regular patterns of Mn porphyrin networks are well-observed regardless of -OEP and -TPP

- **MnOEP-Au(111)**
  - MnOEP-Au(111) 1.4 nm 4 min
  - (Vtip = +0.30 V, t = +0.30 nA, E = No V)

**In situ EC-STM measurement of Au(111) in 0.1 M NaOH**

- **Au lifting**
  - E = -0.4 V
  - E = 0.0 V
  - E = 0.4 V

- **Anion adsorption**
  - E = -0.4 V
  - E = 0.0 V
  - E = 0.4 V

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**Observation of electrocatalytic process on metal center for OER**

- A Plot of the number of oxidized molecules in a fixed 30 nm x 30 nm area of the surface (~900 porphyrins) versus potential at 0.1 V. MnOEP-modified Au(111) shows many protruded Mn porphyrins than MnTPP-modified Au(111).
- The bright species are estimated as Mn(V)/O, Mn(III)-OH or aggregation of Mn porphyrins, as an electrochemical reaction products.
- As expected for initial binding site of OER in alkaline solution, the center of Mn porphyrin shows sharply increased apparent height the

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**Conclusion**

- Two dimensionally well-ordered porphyrin structures are repeatedly observed in the alkaline environment by STM in real-time.
- Porphyrin-modified Au(111) electrodes show much higher efficiency than bare Au(111).
- MnOEP has the highest current density, among the porphyrin-modified electrodes at 0.4 V = Vcomp, which is assumed as Mn oxidation.
- It is suggested that because of its better hydroxide ion adsorption property, MnOEP shows higher performance on OER than MnTPP.
Introduction – CO₂ adsorption on TiO₂(110)

TiO₂ could be used for chemical conversion of CO₂ to other useful molecules because of specific surface properties for photocatalysis. However, a fundamental explanation about the precise mechanism of CO₂ adsorption on TiO₂ is still failed.

• Rutile TiO₂(110) is one of the available choices for the model catalyst samples to investigate the interaction between TiO₂ surface and CO₂ molecules. It is because TiO₂(110) is the most stable form of titania, and it has been widely studied.

• Near-ambient pressure scanning tunneling microscope (STM) is used to investigate changes of TiO₂(110) surface produced by CO₂.

• Preventing water contamination
• TiO₂(110) should not interact with water that could prohibit CO₂ from adsorbing on TiO₂(110) surface.
• Liquid nitrogen cold trap could hold water molecules before the molecules enter on the scanner reaction cell.

• Cleaning cycle
• Repeat this cycle until get clean and reduced TiO₂(110) surface in UHV

Experimental

STM images of TiO₂(110) surface under CO₂ gas condition

Atom size structure of TiO₂(110)

• TiO₂(110) surface has two kinds of rows. One is bridging oxygen(Ob) rows, the light lines, and the other one is titanium(Ti5f) rows, the dark lines.
• Clean and reduced TiO₂(110) surface has point defects such as oxygen vacancies (Vo) and adsorbed hydroxyl(OHb) on Ob rows.

Identifying adsorption configuration of CO₂ on Ti5f rows

• Until CO₂ 10⁻² Torr, defects on Ob decreased slowly, and CO₂ overlayers on Ti5f increased very little. However, When CO₂ pressure reached 10⁻¹ Torr, defects on Ob disappeared quickly, and superstructures of CO₂ overlayers increased dramatically.
• The pressure of CO₂ is a key factor inducing the interaction of CO₂ and TiO₂.

Well ordered domain by adsorbed CO₂

• Identifying adsorption configuration of CO₂ on Ti5f rows
• When adsorbed CO₂ appeared, a center of the bright protrusion by CO₂ located on top of single Ti atom on Ti₅f row.
• Adsorbed CO₂ could diffuse along Ti₅f rows. This means that physisorption induces adsorption of CO₂ overlayers.
• Currently, theoretical calculation on these adsorption configurations has been studied.

Height profiles under UHV and ambient condition

• There were some oxygen vacancies and adsorbed hydroxyl, which located on O₃ rows under UHV.
• STM image of CO₂ 10⁻¹ Torr was significantly different from the image of UHV. Under the CO₂ ambient condition, some bright protrusion having high height appeared on Ti₅f rows.

STM images of TiO₂(110) surface under high pressure

• When pressure reached 1 Torr, it was impossible to identify atomic resolution of surface because of the fast diffusion of CO₂ gas.
• Adsorbates remained on Ti₅f rows, after evacuation from 1 Torr. And defects on O₃ weren’t observed on the evacuation image.

Conclusion

• In this study, we observed that clean and reduced TiO₂(110) surface interacts with CO₂ molecules at room temperature. CO₂ pressure is key factor for the interaction between CO₂ and TiO₂(110).
• CO₂ molecules adsorbed on top of single Ti₅f atom under near-ambient pressure conditions. Superstructures of CO₂ overlayers could diffuse along Ti₅f rows, which means that the origin of the interaction is the physisorption of CO₂. Also, we present three possible adsorption coordination between Ti₅f atoms and CO₂ molecules.
• It is almost impossible to achieve 1 ML coverage image by STM because of the diffusion of gaseous CO₂ molecules. CO₂ adsorbates remained on TiO₂(110) surface after evacuation.

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