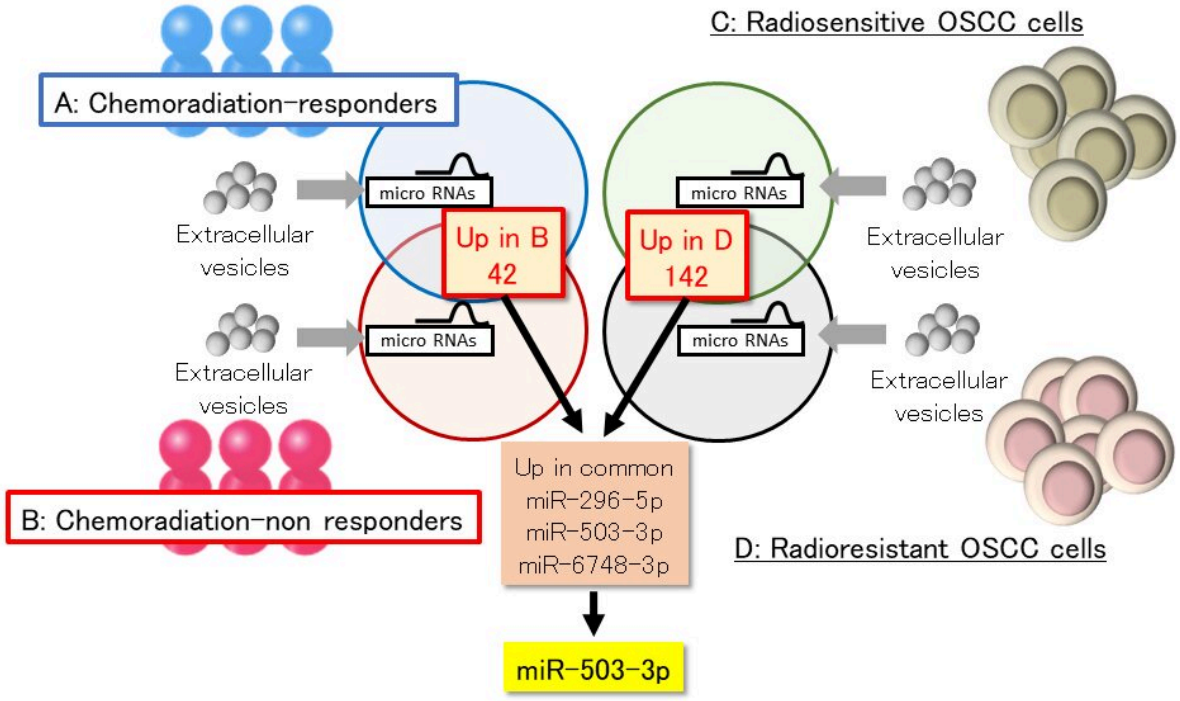
How oral cancer acquires radioresistance

December 16 2021



(Left) The expression levels of microRNAs in extracellular vesicles extracted from chemoradiation-responder and chemoradiation-non responder patients were compared, and 42 microRNAs were picked up that were elevated in the inactive patients. (Right) The expression levels of microRNAs in extracellular vesicles extracted from radiation-sensitive and radiation-resistant cells were compared, and 142 microRNAs were picked up. (Mid-bottom) Preliminary experiments were conducted using three macroRNAs whose expression was up-regulated in both, and finally miR-503-3p was identified as a microRNA involved in radioresistance. Credit: Kumamoto University

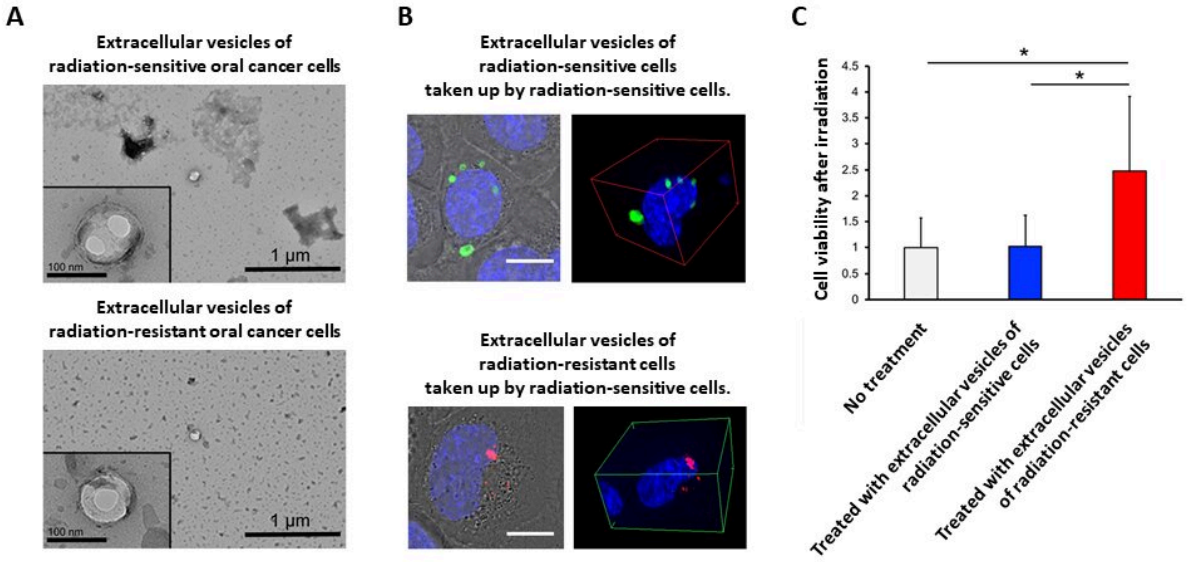
A research group led by Associate Professor Ryoji Yoshida and Professor Hideki Nakayama from the Department of Oral and Maxillofacial Surgery in Kumamoto University (Japan) has analyzed the extracellular vesicles (EVs) of radiation-resistant oral cancer cells and the microRNA contained within them, and discovered a new mechanism by which microRNA imparts radioresistance to surrounding radiation-sensitive oral cancer cells. The researchers believe that that their discovery may lead to the development of new diagnosis and treatment methods for radiation-resistant oral cancer.

Radiation therapy is the second most used treatment, after surgery, for oral cancer. However, some oral cancers are resistant to radiation therapy and may recur or worsen. The prognosis for patients with radiation resistant oral cancer is poor.

Cancer cells are believed to acquire radiation treatment resistance by "talking to each other" using a form of cell-to-cell communication to share various information. The focus of most research has been on EVs, which are released outside the cell, as the cellular communications toolbox because they contain a large amount of information in the form of genes and proteins. Furthermore, little research has been done on the relationship between EVs and oral cancer radiotherapy resistance.

In what they believe to be a world first, the Yoshida & Nakayama research group successfully isolated EVs released from radiation-resistant oral cancer cells. These EVs were then added to radiation-sensitive oral cancer cells which revealed that radioresistance was acquired by radiation-sensitive cancer cells through the transfer of microRNA, one of the pieces of information contained within the EV toolbox. The microRNA (miR-503-3p) is able to suppress apoptosis (cell death) after irradiation, thereby making the formally radiation-sensitive cells radioresistant. The researchers believe that this mechanism highly contributes to the establishment of radioresistant oral cancer within the

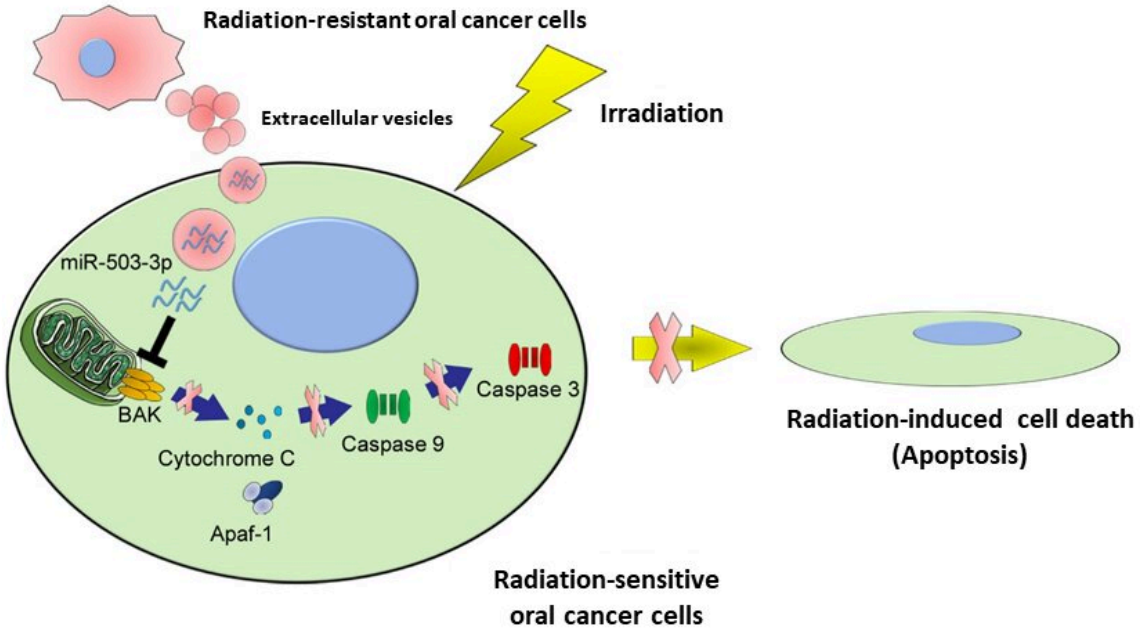
body.



(A) Transmission electron microscopy images of extracellular vesicles isolated from radiation-sensitive (top) and radiation-resisitant (bottom) cells. The lower left square is a magnified image. (B) Fluorescence microscopy images of extracellular vesicles taken up by radiation-sensitive cells. Upper: Extracellular vesicles derived from radiation-sensitive cell (green) are incorporated into a radiation-sensitive cell (blue). Lower: Extracellular vesicles derived from a radiation-resistant cell (red) are incorporated into a radiation-sensitive cell (blue). (C) Change in radioresistance when extracellular vesicles are incorporated into a radiation-sensitive cell. The graphs show the cell viability under each condition. Gray: no treatment, Blue: treated with extracellular vesicles of radiation-sensitive cells, Red: treated with extracellular vesicles of radiation-resistant cells. Credit: From Figs. 1D, 2D & 2E of Yamana K., et.al., *Journal of Extracellular Vesicles*, 2021, CC BY-NC 4.0

Additionally, oral cancer patients with high expression levels of the miR-503-3p microRNA in their blood had poorer treatment effects and

a worse prognosis. In other words, the researchers found that the amount of microRNA in the blood may predict both the therapeutic effect and the prognosis of radiotherapy in oral cancer patients.



Extracellular vesicles released from radiation-resistant oral cancer cells are taken up by radiation-sensitive cells, which release miR-503-3p. The released miR-503-3p suppresses BAK, a protein that promotes apoptosis, thereby preventing radiation-induced cell death (apoptosis). As a result, radiation-sensitive cells acquire radioresistant. Credit: Yamana K., et.al., *Journal of Extracellular Vesicles*, 2021, CC BY-NC 4.0

On uncovering this new mechanism for radiation resistance acquisition by oral cancer, Professor Nakayama said, "Our research may lead to the development of new diagnostic and therapeutic methods for this type of cancer. We hope to soon begin animal experiments with the goal of

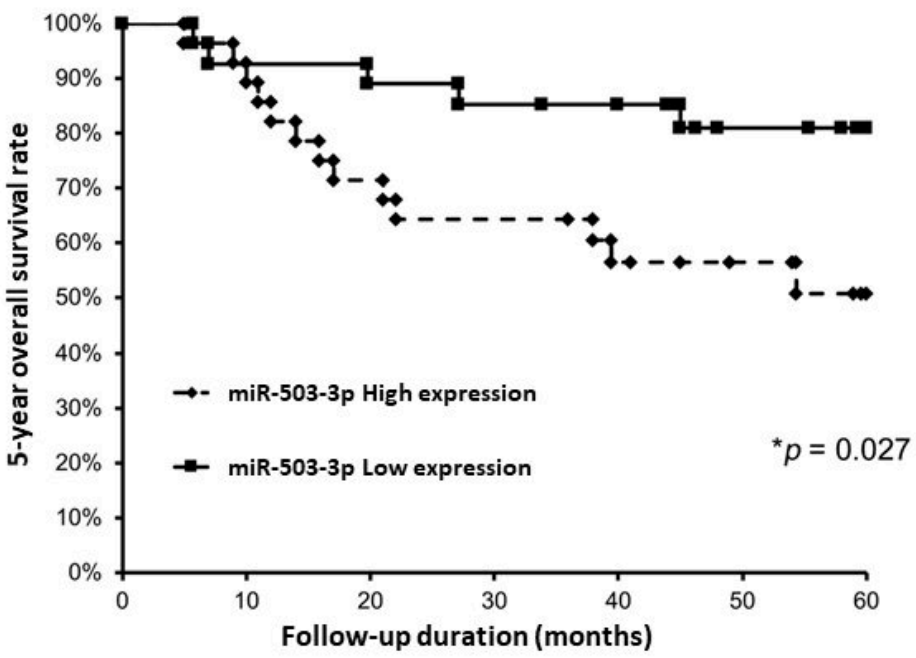
developing a therapeutic strategy that targets the EVs secreted by radioresistant oral cancer."

A

Correlation between the miR-503-3p expression and therapeutic effects of radiotherapy

Characteristic	Total	miR-503-3p expression		*p* -value
		High	Low	
		n (%)	n (%)	
Therapeutic effects of radiotherapy				
Grade I, IIa (poor response)	12	8 (66.7)	4 (33.3)	0.003**
Grade IIb (partical response)	13	6 (46.1)	7 (53.9)	
Grade ≧ III (complete response)	30	14 (46.7)	16 (53.3)	

B



(A) Relationship between the expression level of miR-503-3p and radiotherapy effect. Patients with high expression level of miR-503-3p have poor treatment effect (red underlined area). (B) Relationship between miR-503-3p expression level and patient prognosis. 5-year survival rate is significantly lower in patients with high miR-503-3p expression level (dashed line). Credit: Yamana K., et.al.,

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More information: Keisuke Yamana et al, Extracellular vesicles derived from radioresistant oral squamous cell carcinoma cells contribute to the acquisition of radioresistance via the miR-503-3p-BAK axis, *Journal of Extracellular Vesicles* (2021). DOI: 10.1002/jev2.12169