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Plasma application will open the research to analyze life activity directly observed using an optical microscope by electron microscope.

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Though electron microscopes (EM) are essential for materials science and microstructural analysis, their broader application in medical and life sciences has remained limited due to the complexity of transitioning from conventional optical microscopy (OM) to EM for cellular and tissue imaging. Transmission electron microscopy (TEM) provides nanometer-scale resolution of subcellular structures, such as nuclei, mitochondria, and secretory granules, but it poses significant challenges in routine biomedical workflows. The requirement for additional sample preparation when working with epoxy resin and creating ultrathin sections compromises the integrity and spatial continuity of the tissue and involves time-consuming and technically challenging procedures. Thus, EM analysis does not seamlessly integrate into the standard diagnostic workflow, which typically begins with optical microscopy (OM).

Surface Electron Microscope (SEM) offers broader operational flexibility than TEM due to the large-area imaging capability with nanometer-scale resolution. However, the use of this technique on FFPE tissues is significantly limited due to the high dielectric properties of biological specimens, which reduce the generation of secondary electron (SE) signals. In conventional FFPE sections mounted on glass slides, SEM imaging typically relies on backscattered electron (BSE) detection, which limits spatial resolution and fails to capture nanoscale biological structures such as virus particles (~100–200 nm). Indeed, SEM has sufficient sensitivity to visualize larger pathogens like bacteria and fungi, while direct visualization of viral structures in standard histological specimens has remained elusive.

To address this limitation, we have developed a novel plasma surface processing technology that forms a nitrogen-containing amorphous carbon layer directly on the surface of FFPE sections mounted on glass slides[1-3]. In particular, inspired by Professor Hideo Shirakawa's foundational research on conductive polymers and halogen vapor oxidation, this technique imparts electrical conductivity to inherently insulating biological tissues. By transforming their dielectric surface properties, the modified tissue sections permit efficient SE signal emission, enabling high-resolution SEM imaging directly on standard pathological slides without altering sample preparation workflows.

This breakthrough not only bridges the gap between OM and SEM but also enables the integration of advanced imaging modalities such as immunoelectron microscopy and energy-dispersive X-ray spectroscopy (EDX) on the same FFPE samples. This integration facilitates precise elemental mapping and immunolabeling at the nanoscale, significantly enhancing diagnostic resolution. Notably, we have successfully visualized SARS-CoV-2 viral particles within the vascular walls of pulmonary arteries in autopsy FFPE specimens, achieving direct correlative imaging between histopathological and ultrastructural observations.

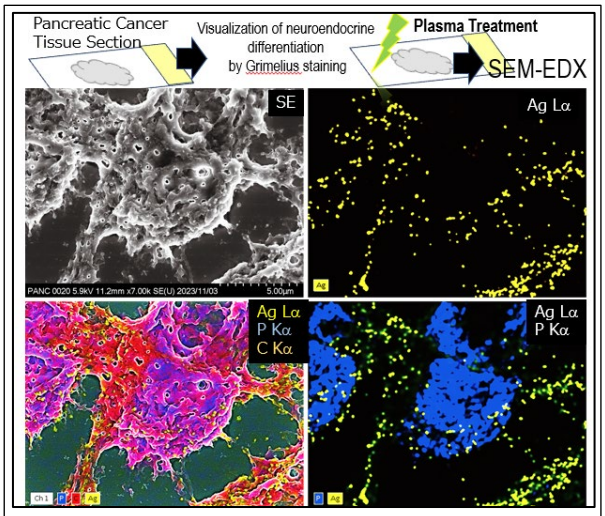

Figure 1. SEM-EDX analysis of plasma-treated pancreatic cancer tissue for neuroendocrine differentiation. Elemental mapping shows AgLα (yellow), PKα (blue), and CKα (red). Tumor nuclei and cytoplasm arevisualized by PKα and CKα, respectively, while neuroendocrine granules are detected as AgLα signals.

In this presentation, we will discuss the interdisciplinary development of this platform that leverages plasma physics, conductive polymer chemistry, and electron optics. We will also highlight its diagnostic potential, particularly in virology and infectious disease pathology, and explore future directions in expanding the utility of electron microscopy in translational and clinical biomedical research.

References

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