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CHANGING SCENARIO IN ORAL PATHOLOGY

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ABSTRACT

This review article covers the current research areas in oral pathology and reflects the broad range that encompasses the development and application of software in digital histopathology, implementation of biomarkers in pathology, genetics and epigenetics. Molecular pathology, regenerative medicine and immuno therapy, holds the promising and optimistic future of pathology. Oral and maxillofacial pathology is standing at the forefront of the revolution and new diagnostic tools and knowledge are taking pathologists into broader roles of research and correlating diagnoses for clinicians. While we are still using the same method and material that has been using for the past 100years, it's time to change. Digital technologies could push the field into becoming more efficient and more scalable. Utilizing

high-throughput, automated digital pathology scanners, it is possible to capture an entire glass slide, under bright field or fluorescent conditions, at a magnification comparable to a microscope. Digital slides can be shared over networks using specialized digital pathology software applications. The future of digital pathology could eventually encompass enhanced

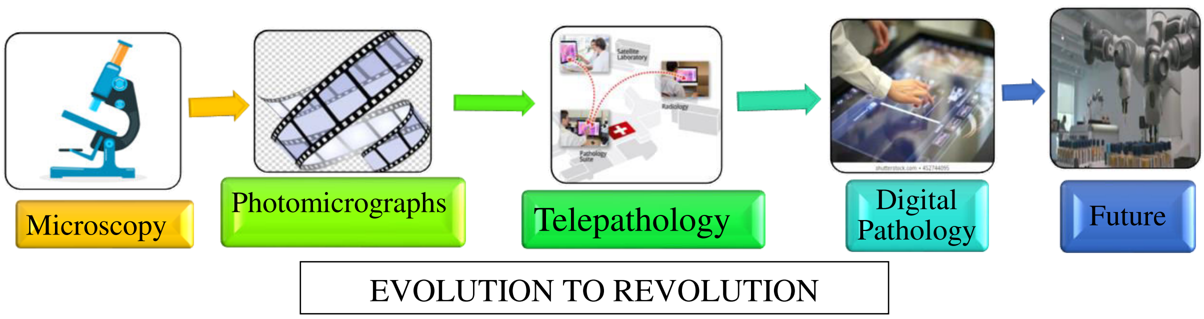
translational research, computer aided diagnosis (CAD) and personalized medicine.
Keywords-Artificial intelligence, whole slide imaging, molecular pathology, nanoparticles, proteomics, next generation sequencing.

INTRODUCTION

Oral pathology is the only branch in dentistry that act as a bridge between clinical sciences and basic sciences, particularly molecular biology. It guides a new pathway for oral healthcare research work along with the special skill for histopathology and cytopathology. Today when the whole world is transforming into a digital hub,we must incorporate this algorithm in our speciality. Digital technologies could push the field of oral pathology in becoming more efficient and more scalable. They could transmogrify the job of pathologists into a more creative and data-driven profession while allowing patients to receive diagnoses faster and more accurately.With the advancement of technology in the field of genetics, molecular biology, regenerative medicines and digital imaging technique,there will be a transformation in our speciality.

HISTORY

Microscope which are the most powerful base and pillars of pathology,was discovered in late 1300.Simple magnifying tube gave birth to the modern microscope. Initially specialized equipment was first used to capture images from a microscope onto photographic plates[1].The conception of tele pathology — transmitting microscope images between remote locations — has been around for nearly 50 years. Although, it is in the past decade that pathology has begun to undergo a true digital transformation, moving away from analog into an electronic environment[1].



DIGITAL PATHOLOGY

Even though the term "digital pathology" has been gaining momentum over the years, digital pathology is just simply pathology. What matters is,the waywe implement it into our laboratories. Itincorporates the acquisition, management, sharing and interpretation of pathology information — including slides and data — in a digital environment. Digital slides are created when glass slides are captured with a scanning device, to provide a high-resolution digital image that can be viewed on a computer screen or mobile device. With more and more laboratories making the transition to digital pathology, incorporation of an innovative tool "artificial intelligence" will provide the key infrastructure in which to deploy AI and their use will start to become a reality in diagnostic practice. The potential of AI in pathology is to create image analysis tools which could either be used for diagnostic support or to derive novel insights into disease biology, in addition to those achievable with a human observer[1].it can be implemented for tumor detection, automated tumour grading, and immunohistochemistry scoring, and predicting mutation status. AI tools can be thought of as being built upon 'expert systems', algorithms that can be given different forms of data, sort and interpret it, and synthesise advice and explanations from this data[1].

Pathologists have been destined to be working in a laboratory in an isolated environment,since many years .But a digitized future can offer them, the ability to work remotely without feeling alone – knowing there is a pathologist in another hospital, perhaps in another country, who is working with you on your case. A synergistic approach that joins up pathologists across the world and accesses the power of AI is the future of pathology. Once a pathologist gets a taste of AI and a digital workflow, they never look back. That's the beauty of digital and of tools like AI.

DIGITAL MICROSCOPY/SLIDES

Histopathology is still completely based on cell and tissue morphology supplemented with in situ molecular information and these together can be studied using an optical microscope.

Digital microscopy creates a digital representation of the whole microscopic slides at decent quality, which can be dynamically viewed, navigated and magnified via a mouse and computer monitor, and shared through computer networks without spatial and temporal limitations[2]. Digital slides can be integrated into the hospital information system (HIS) and accessed through intra- or internet for teaching, primary diagnosis, teleconsultation and quality assurance[2]. Digital slides representing all crucial details of stained tissue sections with decent resolution and high colour fidelity achieved using automated focusing and white balance. Digital slides are consist of giant arrays of rectangular pixels organised along x-y coordinates, each of which is characterised by size, colour and intensity values. Seeing slides on a monitor, with easy access to a computer's multi-functionality, is far more ergonomic than peering through an ocular lens of an optical microscope[2]. Permanent annotations and text put on digital slides, straight measurements of object distance, perimeter or area and prompt still-image archiving at publication quality all support the pathology workflow [1,2]. Several digital slides can be opened side-by-side on the monitor for comparative analysis of serial slides of a sample stained for different biomarkers.

Serial digital slides can also be assembled into a 3-D structure for reconstructing tissue architecture, e.g. to study tumour invasion or re-orient colorectal biopsies. Digital data, including whole digital slides with annotations and measurements, can be integrated into digital databases and shared though intra- or internet with unlimited partners, even simultaneously.With the introduction of digital pathology systems to aid in image-based analysis, the industry is beginning its migration from physical slide sample analysis to digital image analysis.

MOLECULAR PATHOLOGY VISUALISATION

Molecular pathology is a medical subspecialty, increasingly localized between pathology and clinical medicine**.**It got started in the last 10 to 20 years of the last century as a field with the primary goal of aiding pathologists in making the right diagnosis in difficult cases or to find out whether a lesion is neoplastic or reactive. Initially, PCR-based methods were developed that worked on paraffin material allowing the determination of locality of immunoglobulin or T-cell receptor genes in lymphoid neoplasia, or even in nonlymphoid tissues such as myeloid proliferations. In parallel, RT-PCR and later Q-PCR from cDNA or FISH- based techniques became extremely useful methods to look for gene-fusions or for mutations in some diseases. Besides hematology and oncology, a considerable overlap has developed with microbiology, when looking for mycobacteria and other infectious agents in human tissues by PCR, and even with medical genetics, when looking for the diagnosis of hemochromatosis. “Molecular pathology” in recent years is also becoming a tool for basic scientists and, lately for clinicians to look for minimal residual disease, determine prognosis and chose the best therapy.

Various revolutionary progress in human genomics is reshaping our approach to therapy and diagnosis [3].FISH(Fluorescent in situ hybridization) is based on the use of fluorescence-labelled oligonucleotide probes that specifically attach to their complementary DNA sequence target on the genome and label that region with fluorescence color (e.g., Texas red, FITCI green, acridine orange)[3]. The labelled region can then be easily detected under a fluorescence microscope.Fluorescence microscopy detects fluorophores used to label molecules in cells and tissues with the techniques of molecular morphology. Fluorophores are activated at UV or visible wavelength to emit light of lower frequency, usually in blue, green or red, which can be collected through emission filters in a dark background[2, 3].

Instead of using Conventional cytogenetics which is very time consuming, it offers great advantage for the study of chromosomal deletions and translocations and gene amplifications.It can be performed on fresh frozen as well as archival cytologic smears or paraffin-embedded tissue sections. This great versatility, in addition to the topographic advantage of fluorescent microscopic examination, which allows distinction between signals from tumorous and nontumorous cells, has fueled the field of “interphase cytogenetics” in both tumor and a prenatal settings[3].

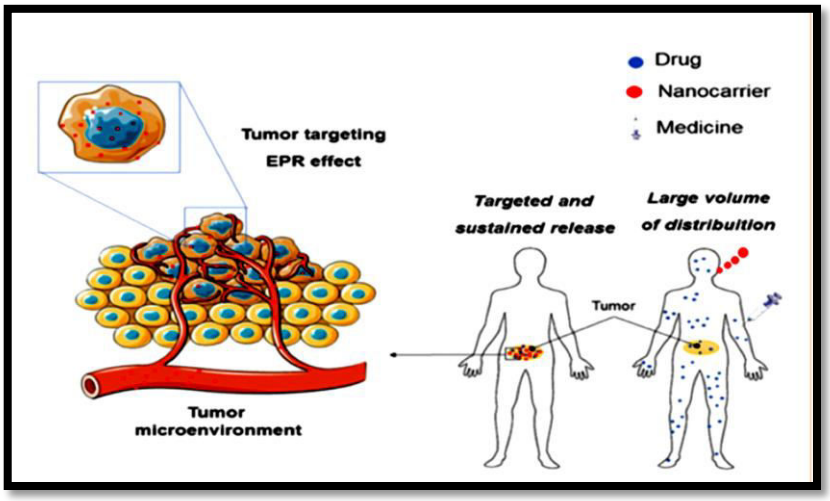
REGENERATIVE MEDICINES (RM)

Oral and maxillofacial pathologist are exclusively the best choice to do the research or contribute to the clinical translation of the same. RM has various avenues to explore such as stem cell therapy, gene therapy, immunotherapy, using growth factors, biomaterials and 3-dimensional (3D) bio printing [4]. Regenerative medicine has the potential to heal or replace tissues and organs damaged by age, disease, or trauma, as well as to normalize congenital defects[5]. Stem cell therapy or cellular therapy involves using autologous or heterologous cells for regeneration by culturing the cells in the laboratory. It will be more fitting for oral pathologists to execute isolation, expansion, characterization and culturing, provided he/she undergo proper training in the affiliatedinstitutions. Designing human-sized organs using scaffolds, especially with 3D bio printing, needs judicious anatomical knowledge [4]. Tooth morphology and oral anatomy being part of our curriculum, the oral pathologist will be naturally a person of choice to create bioengineered or regenerated structures of OMFR.

Immunotherapy or immune enhancement therapy is also gaining lot of attention among the research workers [5]. It is normally custom made for individual patients by isolation of immune cells autologously and propagated for therapeutic purposes to treat cancer. Oral pathologists having good knowledge about oral malignancies can be part of the team designing Immunotherapy strategy ranging from collecting tumor lysate to co-culturing with immune enhancement cells[5].

NANOTECHNOLOGY

In recent years, the application of nanotechnology for cancer has received considerable attention, cutting across various interdisciplinary research areas and is believed to enhance researches focused on cancer detection, diagnosis and treatment [6].It has capability to detect even a single cancerous cell in vivo and deliver the highly toxic drugs to the cancerous cells (Figure 1). Nanoshells, carbon nanotubes, quantum dots, supermagnetic nanoparticles, nanowires, nanodiamonds, dandrimers, and recently synthesized nanosponges are some of the materials used for cancer detection[6].Using specific cross linkers, such as specific antibodies against cancer cells individual cancer cells can be located[6,7]. These materials are very unique in properties such as; size, morphology and distribution.The growing nanotechnology field presents matchless promises in cancer diagnosis over the existing clinical diagnostic devices because nanotechnology substantiates a multilevel diagnosis cutting across tissue imaging, cell imaging to molecular imaging[7].



(Figure 1)Schematic diagram of nanotechnology application in cancer treatment: the nanocarriers passively target the tumour and enhanced the permeability and retention effect of long-circulating polymeric therapy. There is a preferential extravasation of nanocarriers circulation in tumour vasculature. The nanocarriers act either extracellularly or after endocytic internalization once it enters the tumour interstitium (doi: 10.1016/j.heliyon.2020.e04890)

Drug-loaded nanoparticulate system can promote natural key components of immune system (antibodies and cytokines) which simultaneously fight and overcome diseases at the molecular level [7]. This technique provides suitable platform for multimodal, site-specific drug delivery to the tumour sites and increase the survival rate of cancer patients [7].The use of prodrug micelle nanomaterials in cancer treatment is not only restricted to the delivery of drugs into a specific tumour sites,they can also be used in the encapsulation of several smaller molecular compounds due to their properties [7]. In tumour cells or tissues, the nanoparticulate delivery systems enhances the permeability and retention of anticancer drugs than normal tissues.

Green Synthesis ofNanoparticles (NP)

The use of plant materials in the synthesis of NP (biogenic synthesis) is gaining more popularity due to its biocompatible properties which is an important criteria for biomedical applications [8]. Moreover, the production of biocompatible NPs from plant are far more superior than lipid-based vectors such as non-toxic, safe, cost-effective and easily produced accessible materials, prolonged circulating half-life, solubility, high binding affinity, easy functionality, good permeability, controlled pharmacokinetics and ability to protect and safeguard the drug[8]. Green biosynthesis of NPs providesan attractive substitute over chemical and physical methods.The green synthesis of NP is evolving as potential anticancer agent, and they have been discovered as drug carriers and diagnostic agents in diseases treatment due to their predominantly distinctive set of biological, chemical, physical and photonic properties.Both the natural and synthetic NPs find applications in nanodentistry (ND) and maxillofacial pathology (MP) [7, 8].Nanodentistry involves the use of NPs in the development of novel, innovative platforms for dental applications related to diagnosis (for early disease detection), tissue engineering/rejuvenation, drug delivery (local anaesthesia etc.), treatment and maintenance of general oral health care. It provides dentists an alternative approach to tackling oral health challenges with negligible complications and high degree of specificity and therapeutic efficiency. It also assures to save on doctor-patient time and reduce patient mental trauma, while reducing cost. The NP may also be implanted in dental products and interventions to upgrade material properties.The implementation of Nano technological principles and materials has redefined the face of oral diagnosis, therapy, surgery, dentistry and maxillofacial pathologies, globally [8].

LAB-ON-A-CHIP (LOC)

It is a device that integrates one or several laboratory functions on a single integrated circuit (commonly called a "chip") of only millimeters to a few square centimeters to achieve automation and high-throughput screening [9].LOCs can handle extremely small fluid volumes down to less than pico-litres. Lab-on-a-chip devices are a subset of microelectromechanical systems (MEMS) devices and sometimes called "micro total analysis systems" (µTAS) [9]. LOCs may use microfluidics, the physics, manipulation and study of minute amounts of fluids Lab-on-chip technology focuses on the development of hybrid devices, which integrate fluidic and electronic components onto the same chip. Basically lab-on-chip integrate nanomaterial, micro fluidics, Nano sensors, micro electrics, biochemistry, fluidic and electronic components onto the same chip.Research on lab-on-a-chip focuses on several applications including human diagnostics, DNA analysis and, to a lesser extent, the synthesis of chemicals.Future advancements in lab-on-a-chip technology will always depend on at least two major scientific disciplines - microfluidics, and molecular biology. Nanotechnology will play a key role in tying these two fields together as the technology progresses. Despite the hurdles always associated with commercialization of a new technology, viable examples of these devices are beginning to appear on the market. It seems that lab-on-a-chip technology will become increasingly important in the coming years, both in the medical world and in the chemical industry.

<u>APPLICATION OF LAB ON CHIP</u>

- Molecular Biology-It provides a whole new world of opportunities for DNA & RNA sequencing(Figure 2).

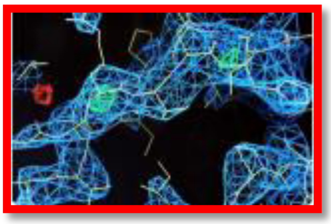


Figure -2

- Proteomics-It provides the opportunity to perform protein analysis while integrating all the steps within the same chip: extraction from the cell, separation by electrophoresis, digestion and analysis using mass spectrometry. These integrated processes show the ability to greatly shorten protein analysis from hours, with macroscopic system, to a few minutes with lab-on-a-chip devices.
- Cell biology-It has ability to control cells at the single-cell level while dealing with a large number of them in seconds. At the microscale level, flow switch can be very fast and goes down to just tens of milliseconds. It can detect and isolate a given cell, such as cancerous cell made fluorescent using antibodies with high throughput. There are several other applications for lab-on-a-chip in cell biology, including micro patch clamp, control of stem cell differentiation, high-speed flow cytometry and cell sorting.
- Chemical laboratories-They have got ability to perform fast heating and cooling at the microscale allows for higher efficiency in some chemical reactions. Therefore, much research has been conducted on using labs-on-a-chip as micro sized and highly parallelized micro chemical reactors.

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COMPUTER AIDED DIAGNOSIS(CAD)

Several solutions have been implemented to resolve the problem of increase in workload and to reduce the existing inter-observer variability. Since then likelihood to digitalise histology slides, groups have applied automated pattern recognition software to identify suspicious features. The so-called CAD systems have been proposed to support pathologist in their decision-making. These systems can automatically measure the extent of malignancy, the grade of the cancer, and generate localized cancer maps.Initially, CAD systems used mathematical algorithms based on structural hand-crafted features or variations in pixel intensities [10].In Current scenario, the majority of CAD systems target on prostate biopsies and high accuracy levels are found in the detection of prostate cancer. In the grading, however, these systems seems to be less correct. An explanation should be the focused on the glandular structures, where the adenocarcinoma emerges. In high-grade tumors, there is an absence of glandular structure and loss of differentiation and thus no structures to detect [10].

ROBOTIC PATHOLOGY

Diseases like cancer have complex tissue morphology requiring microscopic examination [11]. Typically, this involves 2D examination through a microscope by a pathologist, a slow and manual process and does not reveal 3D structures. 3D serial section microscopy has proven to be a powerful tool in examining the 3-dimensional nature of tissue; however, it is limited by the size of tissue samples that can be used and the manual process of acquiring data [11].

The Knife-Edge Scanning Microscope (KESM) acquisition and analysis computational system resolves these problems by creating high resolution light microscopy image data at multi-cubic centimetre scale [11]. Using this system for quantification of microvasculature provides the ability to examine, measure, and compare the 3-dimensional nature of vascular networks at whole organ scale and sub-micron resolution.

NEXT GENERATION SEQUENCING (NGS)

Next generation sequencing (NGS), massively parallel or deep sequencing are related terms that describe a DNA sequencing technology which has innovative result in genomic research [12]. Using NGS an entire human genome can be sequenced within one day.

The main application of NGS in microbiology is to substitute conventional characterisation of pathogens by morphology, staining properties and metabolic criteria with a genomic definition of pathogens. The genomes of pathogens define what they are, may harvest information about drug sensitivity and inform the relationship of different pathogens with each other which can be used to trace sources of infection outbreaks. It has got application in oncology as well. As we all know cancer is caused by somatically acquired mutations, and consequently it is a disease of the genome. With the application of NGS,cancer genomes can now be systemically studied in their entirety, an endeavour ongoing via several large scale cancer genome projects around the world.NGS has got huge potential but currently it is used in research fields only.

CONCLUSION

Oral Pathology has its uniqueness in itself. As an oral pathologist –one can be a clinical specialist, a researcher or academician or an entrepreneur to start an own company to take forward oral healthcare research industry from lab to bench. In my branch of histopathology, my prediction for future is that of diagnostic macroscopy and microscopy will develop alongside of molecular pathology, rather than as a substitute.We should encourage studies that are robust, powerful and demonstrate clinical effectiveness.In future more research should be focused on cancer prognostic markers and cancer cures via targeted therapies. Advances in molecular taxonomy will be an important adjunct to histologic diagnoses. Development of dedicated tissue banks, construction of tissue microarrays, standardization of processing protocols so that paraffinised archival tissue can be effectively harnessed for immunohistochemical and molecular research, all occurring within an established ethical framework that ensures moral standards, will be in the future of research pathology.

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