Laboratory Investigation (2022) 102, 330–331

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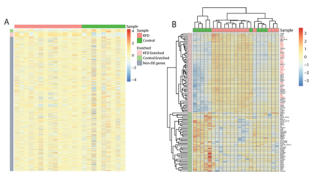
https://doi.org/10.1038/s41374-022-00775-x

MODERN PATHOLOGY

Comparative review of Kikuchi-Fujimoto disease and Castleman disease

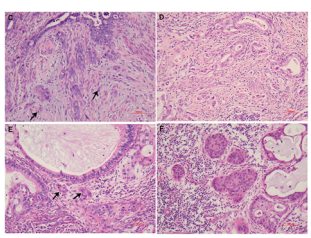
https://doi.org/10.1038/s41379-021-00992-7
https://doi.org/10.1038/s41379-021-00950-3



Li et al. and Wing et al. investigated the molecular basis of two mysterious 'reactive' types of lymphadenitis using a transcriptomics and systems biology approach. Li et al. performed targeted RNA sequencing of 2003 genes associated with immune response in Kikuchi-Fujimoto disease (KFD). Bioinformatics analysis revealed a strong type I interferon (IFN) signature in KFD as compared with reactive controls. Multiple steps of the IFN response pathway were strongly upregulated and correlated with increased numbers of plasmacytoid dendritic cells, histiocytes, and T cells. The findings suggest that KFD is a type I interferonopathy that may be similar to systemic lupus erythematosus. Similar transcriptomics studies revealed completely different findings in Castleman disease (CD). Wing et al. reported that unicentric CD (UCD) and multicentric CD (MCD) showed activation of follicular dendritic cell markers and angiogenesis factors. UCD showed unique upregulation of extracellular matrix remodeling pathway–associated genes whereas MCD was associated with upregulation of IL-6 pathway–associated genes. The findings highlight the ability of transcriptomics approaches to evaluate the molecular basis of rare disorders.

Developing a novel grading system for endocervical adenocarcinoma

https://doi.org/10.1038/s41379-021-00936-1

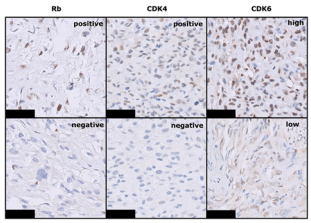


There is no consensus on clinically significant grading criteria in endocervical adenocarcinoma. Shi et al. undertook a novel three-tiered grading system based on tumor budding activity and cell nest size that has been validated as highly prognostic in organ-wide squamous cell carcinomas. The group applied a similar grading system based on tumor budding activity and cell cluster size to assess prognostic value in an institutional cohort of well-annotated endocervical adenocarcinomas consisting of 398 consecutive cases with surgical resection. This system was shown to be robust in prognostic assessment and apparently outperforms conventional FIGO (International Federation of Gynecology and Obstetrics) grading and Silva pattern classification in endocervical adenocarcinoma. The system, if further validated, could be applicable in routine descriptions of endocervical adenocarcinoma.

LABORATORY INVESTIGATION

CDK4/CDK6 inhibition as a novel therapeutic for osteosarcoma

https://doi.org/10.1038/s41374-021-00709-z

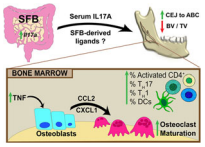


The high-grade bone-forming neoplasm osteosarcoma is known to show chromothripsis, deletions, translocations, and copy number alterations, and the p53 gene and Rb pathways have been most commonly seen. In vivo models using spontaneously transformed murine mesenchymal stem cells (MSCs) were used to show that MSCs with loss not only of p53 but also of $p16^{Ink4a}$, $p16^{Ink4a}$, or $p19^{Arf}$ transform earlier than wild-type MSCs. Across nine models of spontaneously transformed MSCs, these alterations were observed in eight of nine cases. With this shown to be a factor, CDK4/CDK6 inhibitor therapies become a possible option for osteosarcoma treatment. The group demonstrated this using cell culture (two- and three-dimensional) models, with palbociclib proving effective within 72 h. A tissue microarray analysis of 109 primary tumor biopsies revealed a subset of patients (20–23%) with intact Rb but defective p16 or overexpression of CDK4 and/or CDK6. In human trials 45% of patients showed overexpression of CDK6; this correlated with poorer overall survival. Palbociclib is most effective when Rb is intact, which was the case in 53% of the patients with

CDK6 overexpression. Loss of *CDKN2A* and/or *CDKN2B* occurs early in the development of osteosarcoma. The authors propose that CDK4/CDK6 inhibitors could be effective for 20–23% of osteosarcoma patients in the clinic.

The role of the gut microbiota in bone homeostasis

https://doi.org/10.1038/s41374-021-00697-0



Commensal oral microbes elicit local immune responses in barrier gingival epithelial and connective tissues, which modulate osteoimmune signaling and coupled osteoblast–osteoclast actions at the subjacent alveolar bone. Hathaway-Schrader et al. utilized the segmented filamentous bacteria-gnotobiotic mouse model to demonstrate that commensal gut microbes impart systemic immune responses that modify osteoblast–osteoclast crosstalk and skeletal homeostasis in alveolar bone. This work challenges the current paradigm that alveolar bone homeostasis is strictly regulated by oral microbes. Indirect support for the concept that the gut microbiota influences alveolar bone homeostasis is provided by clinical oral manifestations of inflammatory bowel disease (IBD). Inflammatory bowel conditions are linked to dysbiotic shifts in the indigenous gut microbiota. Therefore, progressive alveolar bone loss observed in IBD patients could be influenced by changes in the composition of commensal gut microbes. Future research is needed to determine the utility of noninvasive interventions in the gut microbiota, such as probiotics and prebiotics, to support alveolar bone homeostasis and prevent alveolar bone loss.

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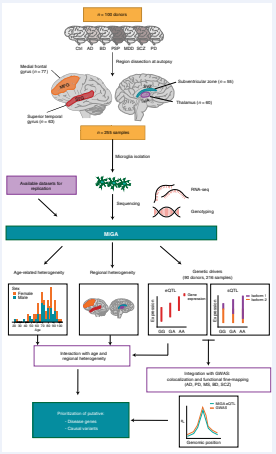
Mapping microglial transcriptome to identify candidate genes in neurodegeneration

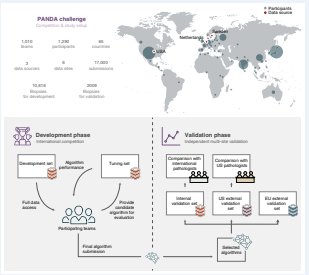
De Paiva Lopes et al. explored the emerging role of microglia in brain aging and pathology. The group performed transcriptome analysis of 255 primary human microglial samples from 100 individuals. Through mapping expression and splicing quantitative trait loci they showed that many neurological disease susceptibility loci are mediated through gene expression or splicing in microglia. Mapping the loci identified candidate causal variants within microglia-specific enhancers; these explorations highlighted microglial expression of *USP6NL* for Alzheimer's disease and *P2RY12* for Parkinson's disease. The authors' comprehensive atlas of genetic effects on the human microglial transcriptome allows identification of potential causal genes and variants underlying risk for neurodegenerative and psychiatric diseases.



Nature Genetics 2022;54:4–17; https://doi.org/10.1038/s41588-021-00976-y

Worldwide validation of AI algorithms for Gleason scoring in prostate cancer

Although artificial intelligence (AI) algorithms for diagnosing prostate cancer are a promising field, they are susceptible to biases in development and validation, and often performance degrades outside the cohort of samples used to develop them. The Prostate cANcer graDe Assessment challenge was developed to address these shortcomings via competition. A total of 1290 developers participated and 10,616 digitized prostate biopsies (now publicly available) were utilized. The developers were isolated from the validation of their algorithms. The developers submitted 34,262 versions of their algorithms, resulting in a total of 32,137,756 predictions made using those algorithms. On US and European validation sets, the algorithms achieved agreements of 0.862 and 0.868 with expert uropathologists and with generalization across factors such as patient population, laboratory, and reference standards. The group confirms that they will attempt to validate AI-based Gleason grading in clinical trials.



Nature Medicine 2022;28:154–163; https://doi.org/10.1038/s41591-021-01620-2

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