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MODERN PATHOLOGY

Immunoregulation of sarcoma

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Seeking to characterize sarcomas in terms of immune biomarkers, Dancsok et al. performed a systematic evaluation of tumor-infiltrating lymphocytes and immune checkpoint biomarker expression in 1072 sarcoma specimens representative of 22 types of sarcoma, along with 236 benign bone and soft-tissue tumors. The more complex the sarcoma type—such as those with complex genomic features (as well as prior exposure to radiotherapy)—had higher numbers of tumor-infiltrating lymphocytes compared with translocation-associated sarcomas (usually associated with simple genomic features). Increased lymphocytic infiltrates were associated with better overall survival among the sarcomas with complex genomic features (those lacking recurrent simple translocations). Co-expression of PD-(L)1 with LAG-3 and/or TIM-3 was seen in high enough proportions to perhaps warrant additional clinical trials targeting these markers in conjunction with PD-1 blockade, along with further exploration of the significance of these markers being expressed together.

Genomic similarities in sarcoma oncogenesis

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Oncogenesis in sarcoma is poorly understood, and a study to investigate the genetic origins of 93 sporadic and 77 post radiation sarcomas provided an opportunity for large-scale analysis of both. Similar chromosomal complexity was observed in the two groups, but *CDKN2A* and *CDKN2B* loss was more prevalent in post-radiation sarcomas than in sporadic sarcomas. Recurrent *MYC* amplifications and *KDR* mutation were found in post-radiation angiosarcomas, consistent with the literature, and the immune response was studied as an actor of tumor aggressiveness. The data did not reveal significant differences in the genetic background of the sarcomas based on their radiation context. The authors propose that further characterization, including whole-genome sequencing, might identify features that distinguish precise differences in oncogenesis. They further postulate that radiation therapies, although known to damage DNA, do not cause mutations that drive oncogenesis.

LABORATORY INVESTIGATION

Reducing scar formation through SnoN

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Sun et al. explored factors in wound healing, with transforming growth factor (TGF)- β 1/Smad signaling as a key regulator. A transcriptional co-repressor of this complex, SnoN (with homology to Ski protein family), was expressed at low levels in hypertrophic scar (HS). SnoN residue (SR) is resistant to TGF- β 1 degradation. Overexpression of full-length SnoN (SF) and SR within wound granulation tissue in a rabbit model of HS reduced wound scarring by inhibiting the transdifferentiation of fibroblasts into myofibroblasts, reducing collagen deposition and arrangement, thereby

attenuating scar hypertrophy. The mechanism for this was amplification of SnoN function in TGF- β 1/Smad signaling due to impairment of degradation. The group suggests SR as a therapeutic target for the prevention of HS following surgeries, burns, or even trauma, and propose further investigation through knockdown models.

Novel biomarker of tumor aggressiveness

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Cancer cells accumulate lipid droplets (LDs), which are involved in intracellular trafficking of cargo proteins. Nardi et al. proposed that LD density increases with tumor aggressiveness in conjunction with V-ATPase. Analysis of LD density in human prostate cancer specimens with Gleason scores of 6 to 8 confirmed this hypothesis. Highly aggressive cell lines exhibited higher maximum LD velocity (LDVmax) than that of less aggressive cells. Blocking V-ATPase directly (or indirectly, with pigment epithelium-derived factor, PEDF) altered LDVmax in a microtubule-dependent manner. More aggressive cancer cells express less PEDF compared with normal cells, implicating an inhibitory role of PEDF on LD velocities. Lower pH in the tumor microenvironment also increased LDVmax in cancer cells. The study thus identified V-ATPase and PEDF as new modulators of LD trafficking.

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Evolutionary cancer genomics and patient outcomes

Next-generation sequencing provides a snapshot of the genetic landscape of cancer and is driving new insights into evolutionary patterns in cancer development. The vast size of tumor cell populations, along with chromosomal instability and phenotypic plasticity, makes for complex analysis but can be enlightening in understanding cancer progression and therapy failure, predicting tumor behavior, and supporting treatment strategies. In this review, Turajlic and colleagues explore clonal evolution and metastases and the clonal evolution of treatment resistance.

They discuss the idea of a single punctuated evolution leading to a dominant clone versus branched evolution leading, later, to minor subclones and the distinct role each of these concepts would have in resulting metastases. They also examine resistance emerging from pre-existing mutations versus developing from de novo mutations. Evolutionary genomics reveals much about the clonal dynamics of cancer and its impact on patient outcomes.

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Microbes and respiratory health

Investigating the lung microbiota as well as that found in distal sites, such as the intestine, Wypych et al. reviewed data that would shed light on the role of these microorganisms in respiratory health and disease and to elucidate how the two systems communicate.

The group looked not only at the role of the microbiota on disease development but also at ways to manipulate the microbiome in order to combat respiratory disease. Explanations for the rise in prevalence of asthma—the authors' featured example—include the hygiene hypothesis (reduced exposure to environmental microbes), the diet hypothesis (reduced consumption of certain

nutrients), and lifestyle changes (obesity, smoking, and decreased physical exercise). The circulation of microbes provides a clear first mechanism for the gut and the lungs to communicate (gut–lung axis) and suggests ways to influence this system for better investigation of respiratory disease and identification of possible druggable targets.

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Genomic analysis provides insight into targeted therapy

Angus et al. used whole-genome sequencing (WGS) to perform an extensive genomic comparison of paired biopsy specimens from 442 patients' metastatic breast cancer and cognate primary tumors. This revealed overall mutational patterns as well as mutational signatures, enriched on the basis of patient therapy. Tumor mutational burden doubled, mutational signatures shifted, and the frequency of mutation in six known driver genes increased in the metastatic setting. WGS data were used to divide patients into subgroups: 42% of patients with metastatic disease could be matched to a personalized treatment through identification of actionable mutations for which drugs are available, and 58% had no known targetable genomic features. New drugs under investigation, such as phosphoinositide 3-kinase (PIK3CA) inhibitors, could benefit more than 40% of the patients in the study, those with an activating mutation in this gene. The data provide crucial genomic information for identifying appropriate treatment options for these patients.

Nature Genetics 2019;51:1450–1458; <https://doi.org/10.1038/s41588-019-0507-7>