We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

3,900
Open access books available

116,000
International authors and editors

120M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
In 2016, a very impressive report was published describing that osteosarcoma (OS) is the earliest human cancer in the fossil record, dating back 1.7 million years to the Homo ergaster era [1]. This demonstrated that OS is the oldest recognized malignant neoplasm with concrete (no pun intended) evidence. In general, OS is the most common malignant bone tumor and mostly affects children, adolescents, and young adults. OS shows significant genetic instability, resulting in a very complex biology with multifaceted cellular and molecular mechanisms and behaviors. This is the main reason why treatment options are still limited and the prognosis has remained unchanged for several decades, despite significant improvements in the 1980s through advancements in systemic chemotherapy and definitive surgery [2]. The prognosis for patients with relapsed and/or metastatic disease is still quite poor.

The concept of “toward precision medicine” was proposed in 2011 to bring about a new treatment paradigm in which clinicians, researchers, patients, policymakers, the pharmaceutical industry, and health care systems work together to improve human health at all levels—disease prevention, diagnosis, and treatment—through the development of more precise, individualized care [3]. Because of the chaotic genetic background of OS and its lack of treatment options, which still mainly involve radical surgery and non-specific combination chemotherapy, the concept of precision medicine could be the most highly desired platform for patients with OS. This chaos of OS biology probably started 1.7 million or even more years ago.

The complicated genetic background of OS is characterized by an extremely heterogeneous genetic alteration spectrum. The most historical and thoroughly described genetic alterations in patients with OS are aberrations of the tumor suppressors p53 and Rb, which cause hereditary dispositions to Li-Fraumeni syndrome and retinoblastoma, respectively [4]. Because both
the p53 and Rb pathways are involved in cell cycle regulation, other cell cycle regulators such as p16INK4a/p19ARF and MDM2 have also been investigated [5]. These tumor suppressors and their associated pathways are still a staple of research for potential therapeutic targets in patients with OS. However, treatments targeting these pathways thus far have failed to show substantial impact.

Recent advances in next-generation sequencing, including whole-genome sequencing, whole-exome sequencing, and RNA sequencing, have revealed several possible candidate pathways involved in OS development. In a study performed at St. Jude Children’s Research Hospital, Chen et al. [6] reported that next-generation sequencing of pediatric OS specimens revealed recurrent somatic alterations: structural variations and/or single-nucleotide variation in the ATRX and DLG2 genes. Among those, the PI3K/mTOR signaling pathways, including the PTEN, PI3K/Akt, and IGF1/mTOR pathways, have emerged as possible therapeutic targets in patients with OS [7]. A genome-wide siRNA screening with a screen of therapeutically relevant small molecules have identified the dual inhibition of the PI3K-mTOR pathway as a sensitive druggable target in OS [8]. A Sleeping Beauty transposon-based forward genetic screen also highlighted that OS driver genes are enriched in the ERBB, PI3K–AKT–mTOR, MAPK, PTEN, and NF2 signaling pathways [9]. Several specific inhibitors of the PI3K–AKT–mTOR pathway have been developed, and their efficacy against OS has been investigated; some of these inhibitors have already been applied in clinical trials [10].

High-throughput screening technologies, including those that involve microRNA (miRNA), have also had a huge impact on the cancer research field. miRNAs are small non-coding RNAs that play critical roles in the regulation of gene expression at the post-transcriptional level and in the control of cellular processes such as proliferation, differentiation, initiation, and progression of various diseases including cancer. More than 2500 miRNAs have been identified, and many of them function as oncogenes or tumor suppressors that regulate gene and protein expression. Some miRNAs like miR-34a and miR-21, target genes involved in OS development such as the p53 and Rb genes as well as the PI3K/Akt/mTOR, IGF-R1, and MAPK pathways. Some miRNAs could be proposed as potential biomarkers of disease progression and metastasis, and may serve as therapeutic targets for OS [11].

For precise, personalized therapeutic approaches, especially in the prediction of the response to chemotherapy, the establishment of predictive biomarkers is a long-standing goal in OS research. The “-omics” approach at the genome, transcriptome, and proteome levels has been applied to identify the predictive biomarkers of OS, and several potential candidates have been identified [12]. Hagelitner et al. [13] recently identified the association between five-year progression-free survival and five genetic variants [the Fas Ligand (FasL), MutS homologue 2 (MSH2), ATP-binding cassette sub-family C (ABCC5), caspase 3 (CASP3), and cytochrome P450 3A4 (CYP3A4)] using a linkage disequilibrium-based tag single-nucleotide polymorphism strategy. They found that patients with fewer risk alleles showed a more favorable prognosis. They concluded that these pharmacogenetic risk factors might be useful to predict treatment outcomes and to stratify patients, thus allowing for more personalized treatment [13]. Recent studies have also uncovered the important roles of the tumor microenvironment, including tumor stromal cells and extracellular matrices, in the development of OS.
stromal/stem cells (MSCs) or MSC-derived lineage-specific progenitors have long been considered as the cells of origin for certain types of sarcomas, including OS [14]. Additionally, OS development is closely linked to certain oncogenic lesions, such as p53 and Rb deficiency in MSCs, and to bone microenvironment signals such as calcified substrates and bone morphogenetic protein-2 [15]. MSCs are not only the putative cells of origin for sarcomas, but are also thought to be the source of cancer-associated fibroblasts, one of the key players in the tumor microenvironment for cancer progression [16]. Several studies have proposed that the mechanism of the interaction between MSCs and tumor cells could be a potential therapeutic target against OS. A recent study by an Italian group demonstrated that MSCs in the tumor stroma driven by oxidative stress induced by OS cells could be potential modulators of the metabolism of OS cells that underwent mitochondrial biogenesis to increase the mitochondrial activity [17]. The authors suggested that this mutual metabolic reprogramming of OS cells and their stroma could also represent a possible target for OS therapies.

Despite remarkable progress in these fields, the results of studies of specific inhibitors of possible targetable pathways and specific biomarkers have not yet been applicable to the clinical setting. However, continued progress in -omics technology, next-generation sequencing, and high-throughput screening will provide new insights into the pathogenesis of OS and will help to identify novel biomarkers that will contribute to improved therapeutic strategies, prognoses, and quality of life.

The role of immunotherapy has been investigated in both the preclinical and clinical settings in OS. Immunotherapeutic techniques include the use of nonspecific immunomodulators such as muramyl tripeptide phosphatidylethanolamine [18], interferons [19], interleukin-2 [20], adoptive T-cell immunotherapy, vaccines, immunologic checkpoint blockades such as CTLA-4/PD-1 blockade, and oncolytic viral therapy. It is very important to continue the development of immunotherapeutic strategies, especially for patients with metastatic disease in whom effective systemic therapy is not a treatment option.

Advances in imaging modalities, surgical procedures, and neoadjuvant chemotherapy have allowed more limb salvaged and less amputation to be performed. Megaprosthetic replacement has become more popular for limb salvage than any other technique, including the use of allografts and vascularized autografts. However, when preoperative chemotherapy is effective and tumor locates far enough from the joint surface, joint preservation rather than megaprosthetic replacement has been utilized. Joint preservation can be achieved using so-called biological reconstruction methods including allografts, vascularized autografts, and processed autologous bone grafts. Processed autologous bone grafts have been developed to utilize the patient's own diseased bone sterilized by irradiation, pasteurization, and liquid nitrogen freezing. However, precise evaluation and surgical planning are required for joint-preserving reconstruction.

Recent advances in three-dimensional (3D) imaging and printing techniques have already had a significant impact on orthopedic surgery. Especially for musculoskeletal tumor resection and reconstruction, 3D visualization of computed tomographic and magnetic resonance images has become an effective supportive tool for surgical planning and determination of surgical margins. In addition, a precise personalized anatomical model of the surgical site by 3D printing can be created for each patient, and personalized guiding templates fabricated by 3D
printing with computer-assisted designs have been utilized for many orthopedic surgeries, including resection of OS [21]. The jaw, including the mandible and maxilla, is a region where OS is occasionally involved, representing 7% of all cases of OS and 1% of all head and neck malignancies [22]. Although definitive surgery is still the mainstay of jaw OS treatment, precise tumor resection is sometimes difficult to achieve because of the anatomical complexity of the maxillofacial region. In this clinical setting of OS of the jaw, as well as in joint-preserving surgery, 3D imaging and printing techniques will be of great help for precise surgical treatment of OS.

A multi-disciplinary approach is essential for the management of OS. Among many clinical symptoms of OS, pain is the most prominent symptom and sometimes requires multimodal treatments. Recent studies have demonstrated that molecular pathways such as the MAPK and PI3K pathways, which are closely involved in OS development as described earlier, play critical roles in regulating the cell signaling of transient receptor potential vanilloid subfamily member 1 (TRPV1), a nociceptive receptor among peripheral nerve fibers that is closely linked in cancer pain [23, 24]. Therefore, these pathways could be possible targets for both cancer-induced pain as well as OS development.

Comparative oncology approaches through translational research involving rodent, canine, and human, models could provide new insights for OS treatment strategies. Genetically engineered mouse models of OS have been created, such as those exhibiting Cre/LoxP-mediated deletion of p53 and/or Rb [25]. A novel model of OS developed using the Sleeping Beauty transposon mutagenesis system was recently established [9]. These mouse models will be useful to identify new candidate driver genes of OS development. While the incidence of OS in humans is roughly 25 per 10 million cases per year in the US, it is about 15 times more common in dogs. The natural history of OS and the genome-wide expression profiles are very similar between humans and canines OS [26]. Comparative studies using a multi-species approach will be indispensable for OS research and will allow us to identify true driver genes and pathways that will provide novel therapeutic targets and new therapeutic strategies encompassing the fields of chemotherapy, immunotherapy, and surgery.

Precision medicine in the management of OS should be a multidisciplinary effort involving the collaboration of both medical and non-medical professions. Involved individuals should include family members, friends, teachers, and colleagues in the patients’ schools and work places. We hope that the findings provided herein will be helpful for all individuals dealing with OS, including physicians, researchers, and patients and their family members.

Acknowledgments

We thank our families, colleagues, patients, and their family members. We also express our gratitude to all participants in this book, especially Ms. Martina Usljebrka for her tremendous efforts during book editing process.
Author details

Kanya Honoki¹* and Kurt Richard Weiss²

*Address all correspondence to: kahonoki@naramed-u.ac.jp

1 Department of Orthopedic Surgery, Nara Medical University, Kashihara, Japan
2 Division of Musculoskeletal Oncology, Department of Orthopedic Surgery, Cancer Stem Cell Laboratory, School of Medicine, University of Pittsburgh, Pittsburgh, USA

References


