Diagnostic Pathology: Open Access

Chen, Diagn Pathol Open 2015, 1:1
DOI: 10.4172/2476-2024.1000e103

Editorial Diagn Pathol Open

Pathogenesis of Sarcomas

Eleanor Chen*

Department of Pathology, University of Washington, USA

***Corresponding author:** Eleanor Chen, Professor of Pathology, Department of Pathology, University of Washington, USA, Tel: 206-616-9118; Fax: 206-543-3967; E-mail: eleanor2@uw.edu

Received date: October 01, 2015; **Accepted date:** October 03, 2015; **Published date:** October 10, 2015

Introduction

Sarcomas are rare mesenchymal malignant tumors with the incidence of about 50 per million in the general population and about 4,000 deaths every year. Clinical management is surgery with wide resection with or without adjuvant radiation and/or chemotherapy. Treatment options for relapsed or metastatic disease are still very limited. This brief editorial review will provide insights into the pathogenesis of sarcomas in terms of etiology, potential cell of origin and underlying genetic alterations.

Etiology

While the etiology of most sarcomas is unknown, some sarcomas arise in patients with cancer predisposition syndromes. For example, patients with Li Fraumeni syndrome, an autosomal dominant disorder with germline mutations in TP53, have increased susceptibility for cancers including sarcomas such osteosarcoma and rhabdomyosarcoma [1]. Patients with loss-of-heterozygosity mutations in the retinoblastoma (RB) gene are at increased risk for osteosarcoma [2]. Up to 8-13% of patients with Neurofibromatosis type 1 (NF1) will develop malignant peripheral nerve sheath tumor (MPNST) [3]. Patients with Gorlin's syndrome (mutations in PTCH1 gene) [4,5] and Costello syndrome (mutations in HRAS gene) are susceptible for rhabdomyosarcoma [6].

Viral infection has been linked to some sarcomas. Kaposi sarcoma arises from the infection of progenitor or endothelial cell with Kaposi Sarcoma Herpesvirus/Human Herpesvirus-8 (KSHV/HHV8) [7]. Complex interactions between infected cells and dysregulated immune response likely lead to Kaposi sarcoma formation. EBV infection has been linked to the smooth muscle tumors arising in immunodeficiency with three major subtypes identified; human immunodeficiency virus (HIV)-associated, post-transplantation and association with congenital immunodeficiency syndromes [8]. The immunosuppression increases the cancer risk likely due to the lack of immune surveillance to destroy nascent tumor cells, but the underlying mechanism leading to different types of neoplasm remains to be elucidated.

Radiation-induced sarcoma is a well-known treatment-related complication and comprises about 3% of all sarcomas. The median latency is about 10 years post- radiotherapy. A wide range of radiation doses (8 to >60 Gy; median of about 50 Gy) have been reported to be associated with sarcoma formation [9]. Radiation induces genomic instability, resulting in accumulation of deleterious mutations and subsequent increased risk of malignancy. The most common type of radiation-induced sarcoma is undifferentiated pleomorphic sarcoma, not otherwise specified. Other major subtypes include angiosarcoma, leiomyosarcoma and extraskeletal osteosarcoma [9,10]. Radiation-induced sarcomas are aggressive, with prognosis thought to be worse than conventional- type sarcomas.

Cell of origin

Sarcomas likely arise from primitive, stem-cell like precursor cell population with the capacity to differentiate into multiple tissue types. This is evidenced by the subtypes with histologic features of a tissue line of differentiation but arising in locations lacking that specific tissue type, e.g. extraskeletal osteosarcoma and rhabdomyosarcoma in sites lacking skeletal muscle. Based on studies of animal models, several sarcoma types can be generated in a multipotent precursor cell lineage or a distinct cell type. For example, osteosarcoma can be generated by loss of p53 and/or Rb in a multi-potent mesenchymal lineage [11]. Embryonal rhabdomyosarcoma can be generated by adipocyte-restricted activation of sonic hedgehog signaling [12]. Overall, transdifferentiation of mesenchymal progenitor cells is a potential mechanism by which sarcomas can arise in various tissue types distinct from their histologic line of differentiation.

Genetic alterations in sarcomas

Based on genetic alterations, sarcomas can be roughly divided into two major categories; one characterized by complex karyotypes with non-specific chromosomal rearrangements, gains and losses, e.g. myxofibrosarcoma, leiomyosarcoma, and chondrosarcoma and the second characterized by simple karyotypes with specific chromosomal translocation events, e.g. synovial sarcoma, alveolar rhabdomyosarcoma and myxoid liposarcoma, or mutations, e.g. activating KIT mutations in Gastrointestinal Stromal Tumor (GIST). For sarcomas with complex genetic alterations, dysregulation of Rb, p53 and growth-factor mediated signaling pathways is frequently present [13]. A large-scale integrated sequencing, copy number and mRNA expression study of six major soft tissue sarcoma subtypes by Barretina et al. has demonstrated recurrent mutations in a subset of cases within each subtype including some targetable pathways [13]. For example, PIC3CA mutations are associated with activated AKT signaling and poor prognosis in 18% of myxoid/round cell sarcomas. Mutations in NF1 have also been detected in a subset of myxofibrosarcomas and pleomorphic liposarcomas.

As the next generation sequencing technology has been utilized more frequently in elucidating the mutational landscape of cancer genomes, the same strategy should be applied to a wider range of sarcoma subtypes to facilitate identification of potential therapeutic targets as well as molecular signatures for sarcoma pathogenesis. Recently, the Cancer Genome Atlas (TCGA) project will launch large-scale genomic studies on 7 major sarcoma subtypes: dedifferentiated liposarcoma, desmoid tumor, malignant peripheral nerve sheath tumor, myxofibrosarcoma, synovial sarcoma and undifferentiated pleomorphic sarcoma. Novel biological and therapeutic insights will be gained from these studies.

Currently, more than 50 subtypes of sarcomas are described in the current World Health Organization (WHO) bone and soft tissue edition. With advances in molecular technologies integrating mutational and expression profiles of sarcoma genomes, additional sarcoma subtypes will result from molecular-based classifications. Additional molecular data will translate into new prognostic parameters and therapeutic targets.

References

1. Malkin D, Li FP, Strong LC, Fraumeni JF Jr, Nelson CE, et al. (1990) Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 250: 1233-1238.
2. Hansen MF, Koufos A, Gallie BL, Phillips RA, Fodstad O, et al. (1985) Osteosarcoma and retinoblastoma: a shared chromosomal mechanism revealing recessive predisposition. Proc Natl Acad Sci U S A 82: 6216-6220.
3. Evans DG, Baser ME, McGaughran J, Sharif S, Howard E, et al. (2002) Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet 39: 311-314.
4. Bale AE (1997) Variable expressivity of patched mutations in flies and humans. Am J Hum Genet 60: 10-12.
5. Hahn H1, Wojnowski L, Zimmer AM, Hall J, Miller G, et al. (1998) Rhabdomyosarcomas and radiation hypersensitivity in a mouse model of Gorlin syndrome. Nat Med 4: 619-622.
6. Gripp KW, Scott CI Jr, Nicholson L, McDonald-McGinn DM, Ozeran JD, et al. (2002) Five additional Costello syndrome patients with rhabdomyosarcoma: proposal for a tumor screening protocol. Am J Med Genet 108: 80-87.
7. Stürzl M, Blasig C, Schreier A, Neipel F, Hohenadl C, et al. (1997) Expression of HHV-8 latency-associated T0.7 RNA in spindle cells and endothelial cells of AIDS-associated, classical and African Kaposi's sarcoma. Int J Cancer 72: 68-71.
8. Deyrup AT, Lee VK, Hill CE, Cheuk W, Toh HC, et al. (2006) Epstein-Barr virus-associated smooth muscle tumors are distinctive mesenchymal tumors reflecting multiple infection events: a clinicopathologic and molecular analysis of 29 tumors from 19 patients. Am J Surg Pathol 30: 75-82.
9. Patel SR (2000) Radiation-induced sarcoma. Curr Treat Options Oncol 1: 258-261.
10. Kirova YM, Vilcoq JR, Asselain B, Sastre-Garau X, Fourquet A (2005) Radiation- induced sarcomas after radiotherapy for breast carcinoma: a large-scale single- institution review. Cancer 104: 856-863.
11. Lin PP, Pandey MK, Jin F, Raymond AK, Akiyama H, et al. (2009) Targeted mutation of p53 and Rb in mesenchymal cells of the limb bud produces sarcomas in mice. Carcinogenesis 30: 1789-1795.
12. Hatley ME, Tang W, Garcia MR, Finkelstein D, Millay DP, et al. (2012) A mouse model of rhabdomyosarcoma originating from the adipocyte lineage. Cancer Cell 22: 536-546.
13. van de Rijn M, Fletcher JA (2006) Genetics of soft tissue tumors. Annu Rev Pathol 1: 435-466.