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Editorial

Heterogeneity Perspectives of Sarcomas

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Editorial

Connective tissue is widely distributed in the human body to help support the musculoskeletal system and organs. These tissues include blood vessels, bones, cartilage, fat, muscles, nerves, and tendons. Such tissues are subject to malignant tumours when they are exposed to intrinsic or extrinsic carcinogenic factors, termed sarcoma, or fleshy substance [1]. This heterogeneous category of cancer includes more than 100 subgroups involves two main types, osteosarcoma, related to bone and soft tissues which both comprises of approximately 1% of all cancer diagnoses [2]. All types of sarcoma occur in different ages, including infants to adults. Although there are outliers within each type of sarcoma, the most common sarcomas across all ages are rhabdomyosarcoma, Ewing, synovial and liposarcoma [3] (Table 1).

Most of these sarcomas originate from mesenchymal stem cells [4-5]. The mesenchymal neoplasm cells are characterised by different staging, signalling pathways and type of tissue, reflecting the complexity of diagnoses and treatments [6-7]. Researchers have indicated that sarcomas are not an individual disease unlike carcinomas, which may be investigated in a less complex manner [7-10]. The heterogeneity of sarcomas requires a more strategic approach to fully understand tumour biological and physiology perspectives of each individual type of malignant connective tissues [11]. The use of specific animal models is important to demonstrate the actual mechanism of how a cell is developed into an individual sarcoma. The advantage of animal models is that they provide a natural environment to show how the cell proceeds into sarcoma, compared to in vitro approach. It also helps to investigate proteomics for understanding gene expression and cellular functions of proteins, as well as the process of the initiation, promotion and progression of the development of sarcoma. Thus, the major challenges in diagnosis and treatment of sarcomas require interdisciplinary efforts to help identify the diagnostic proteomics profile for various sarcomas. These can contribute to the potential clinical testing, especially at the early stages of sarcomas. Per se much effort is needed to distinguish various abnormal proteins in different connective tissues disorders. Since different sarcomas may overlap in their clinical perspectives, more advanced research should be considered as a major importance which is vital for therapeutic approaches.

Proteins are essential macromolecules that carry different functions within connective tissues and the rest of the body. Human proteins are directly associated with the 20,000-25,000 protein-coding genes [12]. Therefore, the structure of the individual protein is not only associated with primary structure but also with its folding, which determines the secondary, tertiary and quaternary structures. The combinations of these structures are associated with the folding of protein molecules to achieve their proper conformation and function within its complex microenvironment [13]. However, protein misfolding gives rise to abnormal protein, with an abnormal conformation which often leads to revoke its specific physiological vital function. The permanent dysfunction of proteins often results in defecting homeostatic mechanisms, or encourages pathological conditions in normal connective tissues [14-17]. The large efforts of researchers have given significant insights into the molecular features of sarcomas in relation to diagnosis and treatment [18]. It is important to consider both oncogenic mutations and complex genomic rearrangements. These changes often contribute significantly in causing abnormalities of the conformation of the expressed proteins, resulting in a wide range of clinical, histological and molecular characteristics [17, 19-21].

The main molecular pathogenesis that underlines the development of sarcoma is associated with a specific chromosomal translocation, resulting in a fusion gene and subsequently producing fused proteins. Sarcomas can be resulted from different types of fusion (Table 2) to disrupt cell biology via chimeric transcriptional regulation, over expression, or altering signalling by changing cellular localization or activity of a signalling protein [22-23]. To understand the genetic manipulation that leads to sarcomas, it is important to understand the significance of conformational structures of macromolecule, mainly the DNA and the process of the transcription of certain protein. Connective tissues in their complex microenvironments can influence the nature of the chemical structure and function of the macromolecules. Both intrinsic and extrinsic factors may play important roles in chromosomal translocation affecting a certain locus on the DNA but this depends on the susceptibility of the DNA sequence to break, in which cellular stress and transcriptional activity trans activities play a major part in the genomic rearrangements [24]. Various studies have considered that genomic rearrangements are not random but fall into four categories: proximity of chromosomal regions in the nucleus, cellular stress, inappropriate DNA repair or recombination, and DNA sequence and chromatin features [25-26].

Although researchers have identified the genetic abnormality of sarcomas, targeted therapy remains a critical issue. The diversity of these heterogeneous diseases poses challenges related to diagnosis,

Table 1: Most common sarcomas.

Sarcoma	Age (Year)	Subtype
Rhabdomyosarcoma	< 7	tumour of striated muscle
Ewing	10-20	Bone cancer, frequently long bones of legs and arms
Synovial	30-40	Osteoarthritis
Liposarcoma	50-70	malignancy of fat cells

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Table 2: Some examples to chromosomal translocation.

Sarcoma	Translocation	Gene
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(p36;q14)	PAX3-FKHR [27] PAX7-FKHR [28]
Ewing	t(11;22)(q24;q12) t(21;22)(q22;q12) t(7;22)(p22;q12) t(17;22)(q12;q12) t(2;22)(q33;q12) t(16;21)(p11;q22)	EWS-FLI1 [29] EWS-ERG [29-30] EWS-ETV1 [30] EWS-FEV [30] EWS-E1AF [30] FUS-ERG [31]
Synovial	t(X;18)(p11;q11)	SSX1-SYT [32-33] SSX2-SYT [32-33] SSX4-SYT [32-33]
Synovial Liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	TLS-CHOP [34] EWS-CHOP [34]

aggressiveness, and drug resistance [35-38].

Morphology and analyses of gene expression are significant approaches in identifying connective tissue of neoplastic cells. In addition, the grade, size and location of sarcoma, together with the histology can help to prognosticate [39]. In the light of this complexity, an understanding of the pathophysiology of these heterogeneous sarcomas requires multi-discipline researches for developing of additional therapeutic approach, in association with study of the structure and function of mainly chromosomes. The current diagnosis strategy uses the conventional immunohistochemistry and morphology. Although, immunohistochemistry-based diagnosis is often used in sarcomas, it has limitations related to the multi-specificity of most markers and antigenic complexity of many tumour types. Therefore, precise histological analysis is important in studying sarcomas [40-41].

Conclusion

Animal models and interdisciplinary approaches in specifying certain sarcoma may lead to more effective diagnosis and treatments.

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