An Introduction to Stem Cells, their Origin, Location, Hierarchy, Functions & Roles in Neoplasia

Roy Pool, DVM PhD
Emeritus Prof Vet Pathology UC Davis, SVM 1994
Clinical Prof Emeritus Vet Pathobiology TAMU CVMBS 2018

While this author isn't a specialist in Stem cell biology, an understanding of the roles of stem cells in veterinary medicine have become increasingly important as to their roles in spontaneous tissue repair, applications to facilitate reluctant healing processes and in neoplasia. Stem cells were once a fellow cellular component of the three embryonic cell layers: (1) Ectoderm that formed the skin and its appendages, e.g., hair follicles; (2) Mesoderm that forms all of the connective tissues of the body, e.g., body fat, fascia, skeletal muscles, tendons, ligaments and attachments to bones and joint surfaces, bone, bone marrow and joints; and (3) Endoderm that forms the digestive tube beginning with the oral & nasal cavities and their respective extensions as the (a) GI system and abdominal organs and (b) respiratory system and lungs.

Stem cells while initially part of cellular proliferation in the respective 3 embryonic layers, they become increasingly restricted as to their potential for tissue formation relative to their location in different tissue structures where they were left behind, e.g., in fascia, tendons, ligaments, bone and joint structures, during skeletal development. In these differentiating fetal connective structures Nature leaves a "trickle" of so-called "resting" or inactive stem cells behind as their fellow proliferative cells continue to differentiate and form a specific anatomical structure.

Nature has left them behind as a reservoir of cells that can initiate repair should damage occur in that site. Unfortunately, "resting" MSCs may be activated and undergo neoplastic transformation. Transformation results in the formation of tumors with a limited range of histologic features that reflect their stage of differentiation at the time in development when they were left as "resting" cells, i.e., these MSCs have a limited range of tumor types that they can form.

For example, mesodermal stem cells (MSCs) left behind in the developing medullary cavity where mesodermal cells during skeletal development form fibrous stroma in the medullary cavity to house hematopoietic cells arriving from their site of origin in the wall of the yolk sac. However, if damage to the medullary cavity occurs, MSCs when activated to repair damage, they can only form fat cells, produce bone matrix, cartilage, and fibrous tissue. While they cannot form skeletal muscle fibers, tendons, ligaments, synovium, etc., they can form the (1) internal callus in fracture healing or (2) bony walls around medullary abscesses.

However, if these "resting" medullary MSCs are provoked and undergo malignant transformation, they can form osteosarcoma and its many variants, chondrosarcoma, fibrosarcoma. liposarcoma and giant cell tumor of bone but not, e.g., skeletal muscle or synovial tumors.

This Stem Cell Presentation primarily addresses Stem cells of the mesoderm, i. e., MSCS. Stem cell biology of the ectoderm/epidermis and Endodermal abdominal structures are left for colleagues to address.

PPT 1.1 Stem Cell Origin

1.1 Embryologic origin of Stem Cells and their potential for tissue formation

1.2. 3 Embryonic Layers
1.3. Zygote/Morula
1.4. Blastula
1.5. Early gastrulation/Archenteron
1.6. Gastrula Stage 2
1.7. Gastric Tube Completion
1.8. Body Cavities & Organs
1.9. End of Embryonic Development

PPT 2.1. Skeletal Development

2.1. Skeletal Development & Remodeling

2.2. Structures formed by Ectoderm & Mesoderm
2.3. Limb development by AER
2.4. Limbs & Body cavity and organs
2.5. Digits determined by BMP/AER
2.6. MSCs in a limb
2.7. MSC trilineage differentiation
2.8. Cancellous Bone Remodeling Unit
2.9. Hypoxia of Medullary Cavity
2.10. Cortical Bone Remodeling Unit
2.11. Figs. of CBRU
2.12. Blood supply cortex
2.13. MSCs Repair vs Tumor

PPT 3.1 MSC Skeletal Repair

3.1. MSCs Skeletal Repair- 6 examples

3.2. Fx-healing: 2 patterns
3.3. Direct Fx-Healing
3.4. Gap Healing
3.5. Effects Mechanical forces
3.6. MSC Articular MSC healing
3.7. Bilateral Hip Dysplasia X-ray
3.8. Infarcted articular cartilage
3.9. MSCs repair articular surface
3.10. Myosatellite cell repair
3.11. Muscle fiber repair
3.12. Spontaneous muscle repair
3.13. Type-3 tendon repair
3.14. Spontaneous tendon repair
3.15. Gross Ck ligament damage
3.16. Vascular ligament repair
3.17. Bone infarct remodeling
3.18. X-rays healing Infarct

3.19. MSCs repair infarct OK
3.20. Repaired infarct collapses
3.21. Infarct repair neoplastic
3.22. END Part 3 role of stem cells

PPT 4.1-4.2.A-B. Role of MSCs in Neoplasia

4.1. Role of MSCs in Neoplasia
4.1-1 Stem cell "niches"
4.2A-1. Benign & L-Gd Tumors
4.2A-2. Hair follicle niche
4.2A-3. Stem Cell skin tumors
4.2A-4. SC basal skin tumors
4.2.B-1 MSC Superficial skeletal tumors
4.2.B-2. Dermal chondromas
4.2.B-3. 11MSc Periosteal Tumors
4.2.B-4. Gross EQJOssfibroma
4.2.B-5. Hp EQJvOssfibroma
4.2.B-6. Hp EQJvOssfibroma
4.2.B-7. Periosteal Fibsarc Fe
4.2.B-8. K9 Max Fibrosarcoma
4.2.B-9. Gross Max Fibsarc
4.2.B-10 Hp Max Fsc L-Gd
4.2.B-11. Hp Max Fsc H-Gd
4.2.B-12. K9PeriostChondroma
4.2.B-13. Eq PeriostChondroma
4.2.B-14. IMGd PeriostChondsarc
4.2.B-15. Compact Osteoma Jaw
4.2.B-16. Cancellous Osteoma Jaw
4.2.B-17. Parosteal Osc Hum K9
4.2.B-18. Parosteal Osc dTib K9
4.2.B-19. Parosteal Osc dHum Fe
4.2.B-20. MaligParostOscdHum K9
4.2.B-21. Hp lungs met above
4.2.B-22. Parosteal Osc ribs Fe
4.2.B-23. Hp of rib tumor
4.2.B-24. Ossifying Lipoma Fascia K9
4.2.B-25. Hp of lipoma above
4.2.B-26. Periosteal Osc talus K9
4.2.B-27. Hp of above tumor
4.2.B-28. Ossifychondroma U. Bladder
4.2.B-29. Figs. of above tumor
4.2.B-30. Hp of bladder tumor
4.2.B-31. Dx of above tumor
4.2.B-32. End Superficial Tumors

PPT 4.2.C MSC Medullary Tumors

4.2.C-1. MSC Deeper Periosteal & Medullary Tumors
- 4.2.C-2. Osteoblastoma d. Humerus HX
- 4.2.C-3. Radiographs osteoblastoma
- 4.2.C-4. Gross images above
- 4.2.C-5. Hp Mac-X of above
- 4.2.C-6. Hp Low-X of above
- 4.2.C-7. Hp Med-X of above
- 4.2.C-8. Hp High-X of above
- 4.2.C-9. Discussion-1 Osteoblastoma
- 4.2.C-10. Discussion-2 Osteoblastoma
- 4.2.C-11. Poorly diff Osteosarcoma
- 4.2.C-12. Xrays infarcted tumor
- 4.2.C-13. Hp arteriopathy arteriopathy
- 4.2.C-14. Hp poorly diff osteosarcoma
- 4.2.C-15. Nonproductive Osteosarcoma
- 4.2.C-16. Xray of above
- 4.2.C-17. Hp with arteriopathy infarct
- 4.2.C-18. Hp of tumor above
- 4.2.C-19. Productive osteosarcoma d. tibia
- 4.2.C-20. Hp tumor above
- 4.2.C-21. O. blastic osteosarcoma humerus
- 4.2.C-22. O. blastic osteosarcoma ischium
- 4.2.C-23. Hx. O. blastic osteosarcoma tibia
- 4.2.C-24. Xray of above
- 4.2.C-25. Hp of above tumor
- 4.2.C-26. Hx, Chondroblastic osteosarcoma
- 4.2.C-27. Xray and gross images of above
- 4.2.C-28. Hp of lower x of above tumor
- 4.2.C-29. Hp of higher x images of above
- 4.2.C-30. HX. Low-Gd fibroblastic osc.
- 4.2.C-31. Fibroblastic Osc Xray in Low Hp
- 4.2.C-32. Low Hp of above
- 4.2.C-33. High Hp of above
- 4.2.C-34. Hx. High-grade fibroblastic osteosarc
- 4.2.C-35. X-ray and Hp of above tumor
- 4.2.C-36. Hp of above
- 4.2.C-37. Telangiectatic osteosarcoma images
- 4.2.C-38. Hp of above
- 4.2.C-39. Giant cell variant of osteosarcoma
- 4.2.C-40. Comparison Chondrosarc & Osarc.
- 4.2.C-41. Chondrosarcoma of a rib
- 4.2.C-42. Lung with Chondrosarc in aorta
- 4.2.C-43. Chondrosarcoma. d. femur
- 4.2.C-44. Chondrosarc of d. femur and Joint

4.2.C-45. Chondrosarc of ramus mandible
4.2.C-46. Hp nodular pattern in Chondrosarc
4.2.C-47. Hp diffuse pattern in Chondrosarc
4.2.C-48. Hp other patterns in Chondrosarc
4.2.C-49. Fibrosarc of px. Humerus X-ray
4.2.C-50. Hp fibrosarc px, Humerus
4.2.C-51. Hemangiosarcoma d. femur
4.2.C-52. Hp above
4.2.C-53. Giant cell tumor of distal ulna x-rays
4.2.C-54. Hp above
4.2.C-55. Giant cell tumor d. ulna x-ray & Hp
4.2.C-56. Hp above
4.2.C-57. Giant cell tumor shaft d. radius x-rays
4.2.C-58. Hp above
4.2.C-59. Hp above
4.2.C-60. Multilobular tumors of suture lines of skull
4.2.C-61. Discussion of sites and differentials
4.2.C-62. Images: Gross and Hp
4.2.C-63. Images; Gross and Hp
4.2.C-64. Images: Gross, x-ray and Hp
4.2.C-65. Images: Gros and Hp
4.2.C-66. X-ray of metastatic lesion
4.2.C.67. End Part C central mesodermal tumors

PPT 4.2.D-Bone Marrow MSC Tumors

4.2.D-1. MSC -Bone Marrow Stromal Tumors & Hematopoietic Tumors of the Medullary Cavity
4.2.D-2. MSC stromal cells can form fat, fibrous stroma, bone & cartilage as well as tumors of those matrices
4.2.D-3. Review: 12 MSC-derived BM stromal cell disorders & tumors
4.2.D-4. Hp normal fatty & hematopoietic bone marrow
4.2.D-5. Hp MSCs form fibrous tissue, bone and cartilage nodules
4.2.D-6. Hp myelofibrosis in K9
4.2.D-7. Hp inherited myeloid hyperplasia & myelofibrosis in Pygmy Goat
4.2.D-8. MSC-derived bone marrow stromal sarcoma
4.2.D-9. Pleomorphic sarcoma: x-ray and histopathology K9
4.2.D-10. MSC repair cells transform to nascent Osc. in tibial infarct K9
4.2.D-11. Epithelioid osc. x-ray and Hp in K9
4.2.D-12. Epithelioid osc. histologic patterns in K9
4.2.D-13. Carcinosarcoma of d. femur, x-ray and Gross image K9
4.2.D-14. Carcinosarcoma of d. femur, Hp features above K9
4.2.D-15. Carcinosarcoma of d. femur, Hp mixed feature above K9
4.2.D-16. Fatty degeneration in medullary cavity K9
4.2.D-17. Central lipoma of d. tibia x-ray and HP Fe
4.2.D-18. Myelolipoma of entire shaft of humerus, x-ray & Hp Fe

4.2.D-19. Myelolipoma Hp above Fe
4.2.D-20. Tumors of Hematopoietic Bone Marrow: List
4.2.D-21. X-ray examples of 4 types of Hematopoietic BM tumors
4.2.D-22. Lymphosarcoma: Hp examples K9
4.2.D-23. Plasma cell myeloma X-ray and Hp K9
4.2.D-24. Plasma cell myeloma with foci of amyloid & MUM-1+ stain K9
4.2.D-25. End topic slide

PPT 5.1 Vascular Bone Tumors

5.1. Vascular tumors of bone: 13 Examples of Surface, Cortical and Medullary Tumors
5.2. Hp 4 examples of canine arterial mediolysis cause bone infarcts K9
5.3. Hp additional examples of canine arterial mediolysis K9
5.4. Glomus vascular tumor, x-ray of RUIN where Hp tumor was present
5.5. Glomus vascular tumor Hp in this K9 lesion
5.6. Endothelial papillary hyperplasia X-ray, Hp in RUIN lesion in K9
5.7. Cavernous hemangioma X-ray, Hp images at Nut foramen tibia K9
5.8 Hemangioendothelioma in infarct repair x-ray HP of d. tibia K9
5.9 Hemangioendothelioma above Hp
5.10. Hemangioendothelioma Body C-2 infarct Gross image Eq OH mare
5.11. Hemangioendothelioma Body C-2 hp of vertebral tumor
5.12. Hemangioendothelioma Body C-2 hp of pulmonary mets.
5.13. Angioleiomyosarcoma d. femur X-ray, Hp in K9
5.14. Angiomatosis spinal articular process Hp Fe
5.15. Angiomatosis spinal articular process additional Hp Fe
5.16. Aneurysmal bone cyst MT2 LH, x-ray Hp K9
5.17. Additional Hp above
5.18. Hemangiopericytoma d. radius Gross & Hp K9
5.19. Additional Hp above
5.20. Hemangiosarcoma d. femur, X-ray, Hp K9
5.21. Hemangiosarcoma d. tibia, X-ray, Hp Fe
5.22. Additional Hp above
5.23. Central hemangiosarcoma in d. femur x-ray and gross K9
5.24. Hemangiosarcoma d. femur Hp above lesion
5.25. MSC pericyte neoplasm created a High-Gd pleomorphic sarcoma K9
5.26. End Topic Vascular Bone Tumors

PPT 6.1 Oxygen, Bone Biology, Tumors

6.1. Role of Oxygen Tension in bone development and MSC activation
6.2. Oxygen tension and long bone development
6.3. Role in perichondrium > periosteum > nutrient foramen
6.4. Role in primary and secondary centers of ossification
6.5. Endochondral ossification forming cancellous ends and physes
6.6. How hypoxia explains why dogs have 27x bone tumors than man
6.7. Canine arterial mediolysis of a limb of nut artery cause an infarct
6.8. Hp 4 examples of arterial mediolysis

6.9. Hp 4 additional examples of arterial mediolysis
6.10. Role of hypoxia in stimulating resting MSC to repair or form tumors
6.11. Bone Infarct Research Archive collection of infarct repair & tumor K9
6.12. Role of MSCs in Cancellous bone remodeling units
6.13. CancellousBnRemod Unit in infarct repair and bone tumor formation
6.14. Bone Infarct Repair: Successful vs Failure, x-rays in two K9s
6.15. Zonal pattern bone infarct repair with progressive stages of neoplasia
6.16. 18 Spectrum of MSC-derived bone tumors in bone infarcts of dogs
6.17. Low-grade Pleomorphic sarcoma prox. tibia x-ray and Hp K9
6.18. Unclassified High-Gd Pleomorphic Sarcoma px Tibia 3yr K9
6.19. Unclassified High-Gd Pleomorphic Sarcoma px Tibia 7 mo. K9
6.20. Pleomorphic liposarcoma in shaft of humerus of 3yr Fe
6.21. Nascent (early) osteosarcoma X-ray and Hp in infarct 9yr K9
6.22. Low-Gd osteosarcoma X-ray and Hp in infarct 14yr Fe
6.23. Osteosarcoma in infarct d. femur, X-ray, gross and Hp 10yr K9
6.24. Chondroblastic osteosarcoma d. Radius, X-ray, gross and Hp K9
6.25. Giant cell variant osteosarcoma d. Femur, X-ray, gross & Hp K9
6.26. Giant cell variant osteosarcoma px Hum., X-ray, gross & Hp K9
6.27. Chondrosarcoma px shaft hum. X-ray, Hp infarct in K9
6.28. Clear cell chondrosarcoma, d. radius, X-ray, Hp K9
6.29. Myxoid chondrosarcoma in midshaft infarct. X-ray, gross, Hp K9
6.30. Fibrosarcoma, midshaft fx. Femur, X-ray, Hp K9
6.31. Giant cell tumor of bone d. shaft radius, Hp K9
6.32. Hemangioma d. shaft tibia, X-ray, Hp K9
6.33. Hemangiosarcoma d. femur. X-ray, Hp K9
6.34. Two uncommon MSC-derived bone tumors- listed
6.35. Epithelioid osteosarcoma in px. Tibia, X-ray, Hp K9
6.36. Carcinosarcoma d. shaft femur, X-ray, Hp K9
6.37. End Infarct activated MSC-derived bone tumors

PPT 7.1 Joint Formation, Structure, Tumors

7.1. Joint formation. Structure, Function of Lining and Synovial Tumors
7.2. Role of ischemia in joint formation
7.3. Joint cavities with & without intra-articular ligaments
7.4. Two synovial layers, functions, MSC locations, chondromas
7.5. End Top Joint development and structure

PPT 8.1 Joint Trauma, Synovial Tumors

8.1. Traumatic joint lesions covered as (8.2) while Synovial Tumors covered as:
1- Benign Tumors (8.3-8.21)
2- Malignant Tumors of Joints & Tendon sheaths (8.22-8.45)
8.2. Villonodular synovitis d. MCIII X-ray, gross, HP Eq
----------Benign----------
8.3. Pigmented villonodular synovitis. History, hock, K9
8.4. Hp of 3 images of above

8.5. Villonodular synovitis Tendon sheath, gross & Hp Eq
8.6. Hp images of above
8.7. Calcinosis Circumcripta, Goss, tendon sheath and tongue K9
8.8. Tumoral Calcinosis: Described and 3 forms are discussed
8.9. Tumoral calcinosis of bilateral carpal borders, X-rays, K9
8.10. Tumoral calcinosis one of paired hock lesions, X-ray, gross, K9
8.11. Tumoral calcinosis Fibrous capsule shoulder jt. Hp, K9
8.12. Fibroma tendon sheath, Hp, K9
8.13. Hemangiopericytoma tendon-sheath, Gross, K9
8.14. Hp images of above tumor
8.15. Infiltrative myxoma of DDF tendon, Gross & Hp K9
8.16. Giant cell tumor (benign) of tendon sheath, Gross, Fe
8.17. Giant cell tumor (benign) of tendon sheath, Hp, Fe
8.18. Arteriovenous hemangioma tendon sheath, gross, Hp, Fe
8.19. Angiomatosis shoulder joint History Fe
8.20. Angiomatosis shoulder joint. CT images above, Fe
8.21. Hp images of above

----------Malignant----------

8.22. Malignant Synovial Tumors of Joints and Tendon Sheaths: 10 examples
8.23. Malignant Joint vs Tendon Synovial tumors compared
8.24. Synovial sarcomas of joint images 4 X-ray examples K9
8.25. Synovial sarcomas of joint images 4 gross examples K9
8.26. Histologic patterns of synovial sarcomas compared
8.27. Pleocellular pattern, a common Hp pattern K9
8.28. Spindle histologic pattern K9
8.29. Hp example of above K9
8.30. Predominant giant cell synovial sarcoma joint K9
8.31. Biphasic synovial sarcoma X-ray, Gross, Hock Jt. K9
8.32. Hp of above tumor
8.33. Immunostains of above tumor
8.34. Biphasic synovial sarcoma of tendon sheath Hp DDT K9
8.35. Immunostains of above tumor
8.36. Discussion of Biphasic Hp features of tendon sheath sarcomas
8.37. Malignant tendon sheath tumors radiocarpal region X-rays
8.38. Malignant tendon sheath tumor Gross stifle region K9
8.39. Malignant tendon sheath tumor Gross paw K9
8.40. Malignant tendon sheath tumor soft parts Hp K9
8.41. Histiocytic sarcoma of elbow synovium- Discussed Pathogenesis
8.42. Histiocytic sarcoma of elbow synovium X-ray, Hp K9
8.43. Histiocytic sarcoma of elbow synovium Hp K9
8.44. Gross Osteosarcoma incorrectly dx as synovial sarcoma by BN bx
8.45. End synovial tumors of joints and tendon sheaths

PPT 9.1 Synovial Chondromas

9.1. Cartilaginous nodules formed by activated "resting" MSCs in superficial layer of articular cartilage, synovial lining of joints and tendon sheaths, attachments to bone and periarticular joint surfaces and in fascia attached to connective sheaths of tendons and ligaments

9.2. 17 Examples of cartilage nodules formed by activation of "resting" MSCs
9.3. MSCs in tangential layer of articular cartilage can from surface nodules
9.4. Hp examples of articular surface nodules formed by activate MSCs
9.5. Synovial chondromas and osteochondromas pathogenesis discussed
9.6. Gross DJD provoked MSC articular surface and periarticular chondromas
9.7. Hp examples of different stages of formation of synovial chondromas
9.8. Synovial chondromas 2dry to patellar DJD Gross and Hp Eq
9.9. Similar disorder of patella with detachment of nodule and Hp nodule Eq
9.10. Primary synovial chondroma/osteochondroma discussed pathogenesis
9.11. Primary synovial osteochondromatosis X-rays & Hp stifle Fe
9.12. Multicentric synovial osteochondromatosis X-rays K9
9.13. Synovial osteochondromatosis bilateral, History Fe
9.14. Synovial osteochondromatosis bilateral shoulder X-rays, Fe
9.15. Hp above synovial osteochondromas
9.16. Hp other synovial osteochondromas from periarticular nodules
9.17. Viral (c-retro virus) osteochondromatosis, X-ray, gross, TEM Fe
9.18. Intra-capsular and Para-articular chondromas discussed with refs.
9.19. Discussion of role of low O2 in change of oblasts to chondrocytes & MSCs
9.20. Hp images of transformation of tendinocytes to chondrocytes in TBs
9.21. Para-articular chondroma/osteochondromas in elbow, & stifle, X-rays K9
9.22. Para-articular chondromas X-ray and Hp stages of development K9
9.23. Para-articular chondromas X-ray, gross and Hp hock jt. Eq
9.24. Para-articular chondromas X-ray and Hp toe Fe
9.25. Terminology for chondromas arising in fascia of CT attachments
9.26. Paratenon chondromas of DDF tendon of Digit, X-ray & gross K9
9.27. Hp Low x of above specimens
9.28. Hp High x of above specimens
9.29. Para-ligament chondroma branch suspensory ligament, X-ray, gross Eq
9.30. Hp Para-ligament chondromas of above specimen
9.31. Hp Para-ligament chondroma of suspensory ligament of another Eq
9.32. Hp Para-ligament chondromas in suspensory ligament of another Eq
9.33. Myositis ossificans Discussed in Man and Animals
9.34. MO in a mature cat X-rays and Hp
9.35. MO in muscle fascia of elbow attachments X-ray and Hp mature Cat
9.36. MO in intermuscular fascia of shoulder Xray and Gross in mature Cat
9.37. MO Hp of mass, borders and central area in a feline lesion
9.38. MO in muscle fascia in lateral upper forelimb of a mature Dog
9.39. MO in muscle fascia of rt. Flank. Gross & specimen X-ray, 8yr. Eq
9.40. MO Hp figures of entire x-section and borders of above mass
9.41. End of topic of Nodular Masses formed by activation of "resting" MSCS