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REVIEW & HYPOTHESIS

An Etiologic Model Equating Hodgkin and Reed/Sternberg Cells to Maturing Megakaryocytes and Hodgkin's Disease to Extramedullary Hematopoiesis

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Abstract. **Research on a related topic led the author to note the similarity between Hodgkin/Reed-Sternberg (H/RS) cells and megakaryocytes and to hypothesize they may be identical. This possibility was tested by conducting a literature review to collect data on the physical and functional characteristics of the two cell types. The present review revealed that H/RS cells and megakaryocytes share numerous features. Physically H/RS cells resemble immature megakaryocytes. Hodgkin cells possess the large, round nucleus, multiple nucleoli, immature cytoplasm and ability to undergo endomitosis that characterize megakaryoblasts while Reed/Sternberg cells possess the large segmented nucleus, prominent nucleoli and granule producing Golgi apparatus that characterize basophilic megakaryocytes. H/RS cells and megakaryocytes also have similar functional characteristics. Numerous surface receptors on H/RS cells are also present on megakaryocytes. Three signaling cascades that are very active in H/RS cells, MEK/ERK, JAK/STAT and PI3K-AKT, are also active in megakaryocytes. Many transcription factors, such as AP-1, STATs-1,-3,-5,-6 and GATA-2 are active in both H/RS cells and megakaryocytes while the hallmark of H/RS cells, the constitutive activation of the transcription factor NFkB, has recently been observed in megakaryoblasts. Another distinctive trait shared by H/RS cells and megakaryocytes is the transmission of both antiapoptotic and apoptotic signals. These similarities support the hypothesis that H/RS cells are immature megakaryocytes. This, in turn, suggests that Hodgkin's tissue nurtures developing hematopoietic cells and may be extramedullary hematopoietic tissue. Several features of Hodgkin's tissue support this equivalence. If this hypothesis is correct it has important implications for the treatment of Hodgkin's Disease.**

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1. Introduction

Classic Hodgkin's disease (HD) is believed to be a neoplasm of the lymph node consisting of rare and malignant Hodgkin and Reed/Sternberg (H/RS) cells surrounded by a reactive infiltrate of lymphocytes, eosinophils, neutrophils, plasma cells, histiocytes and fibroblasts [1,2]. H/RS cells are thought to arise via genetic mutation, but there is little agreement as to the cell of origin. Lymphocytes [3,4], macrophages [5,6], dendritic cells [7] and interdigitating reticular cells [8] have all been proposed as the cell of origin.

Although most recent research assumes a genetic etiology for HD this is not the only possible explanation for the origin of H/RS cells. Another hypothesis is that they are normal cells in an unusual histological setting. Given their large size and other characteristics the most likely candidate is the megakaryocyte. Physical similarities between H/RS cells and megakaryocytes have been noted for many years. Petrakis et al. [9] and Bayrd et al. [10] both observed that Reed Sternberg (R/S) cells may be confused on morphological grounds with megakaryocytes and Weiss et al. [2] instructed readers to "search for Hodgkin cells in areas of fibrosis as search made in normal marrow can lead to misidentification of hematopoietic precursors or megakaryocytes as Hodgkin cells." While the idea that H/RS cells are megakaryocytes has not been considered for some time, past researchers did observe a close association between HD and megakaryocytes. Bunting [11] noted that Hodgkin's Lymphoma occurred in association with thrombocytosis and although he did not equate H/RS cells to megakaryocytes he noted that "… there is present in the glands, besides the endotheliod giant cells, a type of giant cell indistinguishable from the bone marrow megalokaryocyte". Medlar [12] went further in linking HD and megakaryocytes proposing that "The histopathology of Hodgkin's disease is a pleomorphic aggregation of cells which represent the developmental cycle of the megakaryocyte." When Bunting and Medlar made these observations very little was known about either H/RS cells or megakaryocytes. We now have a better understanding of both cell types and this knowledge strengthens the case for their equivalence.

2. The Presumptive Malignant Cells of HD

The presumptive malignant cells in HD are frequently referred to as a single entity (*i.e.*, H/RS cells); however, there are at least four distinct cellular morphologies: Hodgkin, Reed Sternberg (R/S), Lacunar and Mummified. Detailed descriptions of Hodgkin and Lacunar cells are rare in the literature. For that reason the description of Hodgkin cells in this paper is based primarily on the "Group B" cells delineated by Anagnostou et al. [13], while the description of Lacunar cells is based primarily on their "Group D" cells. Hodgkin, R/S and Lacunar cells are all large, but vary in nuclear shape and cytoplasm content. The Hodgkin cell has a large, frequently round nucleus [14], with one to three prominent nucleoli [13]. Its cytoplasm contains numerous ribosomes and polysomes but only small amounts of smooth and rough ER [13]. The R/S cell, on the other hand, has an indented nucleus [13,15]. These indentations divide the nucleus, which contains a prominent nucleolus [13,15], into segments. The cytoplasm is similar to that in the Hodgkin cell as it contains abundant ribosomes and polysomes, but differs in that it also contains a Golgi complex and granules [13]. While the nucleus of the R/S cell is segmented, the nucleus of the Lacunar cell is divided into lobes and referred to as hyper lobular [13,14]. Detailed descriptions of the cytoplasm are lacking. It has been described simply as "packed with black granules" [13]. The mummified cell consists of a condensed basophilic nucleus [16] surrounded by retracted eosinophilic cytoplasm [2].

3. The Presumptive Malignant Cells of HD are Equated to Maturing Megakaryocytes

TABLE 1. Physical similarities between the presumptive malignant cells of Hodgkin's Disease and maturing megakaryocytes.

	Presumptive Malignant Cells of Hodgkin's Disease	Cells of Megakaryocytic Lineage
Cell Name	***Hodgkin***	***Megakaryoblast***
size	15 – 25 μm [28], 10-25 μm [15]	10 – 24 μm [31]
nucleus	Large, frequently round [14]	Round [32]
nucleoli	1 – 3 [13]	2 – 3 that vary in size [33]
cytoplasm	Numerous ribosomes and polysomes [13]	Ribosomes [17], numerous polysomes [33]
	Small amounts of smooth and rough ER [13]	A few ER [33]
	Lysosome like dense bodies [13]	Lysosomal granules [32]
Cell Name	***Reed/Sternberg***	***Basophilic Megakaryocyte***
size	20 – 30 um [28]	15 – 40 μm [31]
nucleus	Markedly lobated or segmented [29], one or sometimes several indentations [13,15] or deep infolds [6]	Segmented [33], lobulated [32]
nucleolus	Large [6,15] and prominent [13,15]	One or more [32]
cytoplasm	Variable [6] to many ribosomes and polysomes [13,29]	Many polysomes [32,33]
	Moderate to well developed Golgi [6,13]	Prominent Golgi [32,33]
	Golgi associated with prominent membrane bound granules [13,29]	Golgi associated with small azurophilic granules [32,33]
	Microfibrils – near nucleus [6] and around cell center [15]	Microfibrils in border between intermediate and marginal zones [32]
	A few lysosomes [6,15]	Lysosomes [32]
	Glycogen granules [6]	Glycogen content increases with maturation [32]
	Occasional filopodia [6] and cytoplasmic processes [6,15]	Localized pseudopodia [34]
	Numerous long finger-like processes arranged in large indentation of cell surface [15]	Early demarcation membrane system forms in depression of cell surface [34], membranes continuous with plasma membrane [32], form a series of cytoplasmic cylinders [33]
Cell Name	***Lacunar***	***Granular/Proplatelet producing Megakaryocyte***
nucleus	Hyper lobular [13,14] hyper segmented [13]	Highly lobular [32,33], lobes unequal in size joined by large connections [33] or fine chromatin bridge [32,33]
nucleolus	Less prominent than in R/S cells [14], small [13]	Not mentioned in descriptions
cytoplasm	Abundant pale eosinophilic cytoplasm [1], faintly acidophilic [13]	Eosinophilic cytoplasm [31], acidic cytoplasm [32,33]
	Packed with black granules [13]	Numerous azurophilic granules [32]
	A narrow peripheral space with no [6] or few [13] organelles	Outer zone contains glycogen granules, microfilaments and microtubules but free of organelles [17,32]
	Long, thin cytoplasmic processes [30]	Proplatelet formation via elongation of cytoplasmic extensions with central longitudinal bundles of microtubules [35]
Cell Name	***Mummified/Zombie***	***Denuded megakaryocyte***
nucleus	Condensed basophilic nucleus with tortuous contour [16], pyknotic chromatin [2], fuzzy outline [2]	Pyknotic or edematous nucleus [33]
cytoplasm	Deeply eosinophilic retracted cytoplasm [2]	Nucleus enveloped by thin layer of granular cytoplasm [36]

TABLE 2. Cell surface receptors present on both H/RS cells and megakaryoblasts/cytes.

Receptor	H/RS Cells	Megakaryoblasts/cytes
Cytokine Receptors		
IL-3R	Yes [41]	Yes [63]
IL-6R	Yes [42]	Yes [63]
IL-9R	Yes [43]	Yes [64]
IL-11R	Yes [44]	Yes [65]
IL-13R	Yes [45,46]	Yes [66]
Growth Factor Receptors		
VEGFR	Yes [47]	Yes [67]
PDGFR	Yes [48]	Yes [68]
FGF-R2	Yes [49]	Yes [69]
Steroid Receptor		
GATA2 (Estrogen receptor)	Yes [50]	Yes [70,71]
Stromal Cell Ligand Receptors		
c-kit	Yes [51]	Yes [63]
c-met	Yes [52]	Yes [72]
CXCR4	Yes [53]	Yes [73,74]
Extracellular matrix Receptors		
A 4 β 1	Yes [52]	Yes [75,76]
α 5 β 1	Yes [52]	Yes [76]
CD36/DDR2	Yes [48] (DDR2)	Yes [77] (CD36)
Galectin-1	Yes [54,55]	Yes [78]
Apoptotic Ligand Receptors		
CD95 (Fas/APO-1)	Yes [56,57,58,59,60]	Yes [79]
TRAIL R1	Yes [61]	Yes [80]
TRAIL R2	Yes [61]	Yes [80,81]
Cluster of Differentiation		
CD4	Yes [62]	Yes [82,83]

Abbreviations: IL – interleukin; FGF-R2 – fibroblast growth factor receptor -2; PDGFR – platelet derived growth factor receptor; TRAIL – tumor necrosis factor receptor apoptosis inducing ligand; VEGFR – vascular endothelial growth factor receptor.

3.1. The presumptive malignant cells of HD are polyploidal

The most obvious similarity between the presumptive malignant cells of HD and megakaryocytes is large size. Megakaryocytes attain their size via endomitosis, the duplication of DNA without cytokinesis. This process results in a large polyploidal cell with DNA content ranging from 4 to 64 N [17]. H/RS cells also attain their unusually large size via endomitosis. In 1959, Petrakis et al. [9] found that approximately half of the R/S cells examined had a DNA content of 4N or greater leading them to conclude that R/S nuclei undergo endomitosis. More recent studies have since confirmed the polyploidal character of these cells [18,19].

The similarity between megakaryocytes and H/RS cells goes beyond the fact that they are polyploidal to the method of endomitosis. Both cells actually enter mitosis but abort the process following early anaphase [20, 21]. Although the molecular mechanism controlling this process is not known, cyclins D3, E and B may play a role and they are present at elevated levels in both H/RS cells and megakaryocytes [22-27].

3.2. The presumptive malignant cells of HD are physically similar to maturing megakaryocytes

TABLE 3. Physical similarities between the presumptive malignant cells of Hodgkin's Disease and maturing megakaryocytes (all abbreviations are provided on next page).

Feature	H/RS Cells	Megakaryoblasts/cytes
Important Signaling Pathways		
MAPK (MEK/ERK)	Yes [61]	Yes [73,116,117,118]
PI-3K-AKT	Yes [87]	Yes [73,119]
Jak/Stat	Yes [84,85,86]	Yes [120]
Active Transcription Factors		
NF*k*B		
p50 – p65 (Rel A)	Yes [88,89,90]	Yes [121,122]
p50 – p50	Yes [89,91]	Yes [121]
AP-1		
Complexes containing c-Jun	Yes [92]	Yes [123]
Complexes containing c-Fos	Yes [92]	Yes [123]
STAT		
Complexes containing STAT1	Yes [22,93]	Yes [73]
Complexes containing STAT3	Yes [22,84,85,93]	Yes [73,120]
Complexes containing STAT5	Yes [84,86,94]	Yes [73,120]
Complexes containing STAT6	Yes [84]	Yes [73]
GATA-2	Yes [50]	Yes [70,71]
NFAT-1	Yes [95]	Yes [124]
p53	Yes [62,96.97]	Yes [125]
p21	Yes [96,97]	Yes [26]
Synthesis of Cytokines		
IL-1	Yes [8,98]	Yes [126,127]
IL-3	Yes [62]	Yes [126]
IL-6	Yes [42,44]	Yes [126,127]
IL-13	Yes [45,46,94]	Yes [128]
TNFα	Yes [56,99]	Yes [127,129]
Synthesis of Growth Factors		
TGF-β	Yes [100]	Yes [129]
FGF2 (basic)	Yes [49]	Yes [129]
VEGF	Yes [47,101]	Yes [67,129]
PDGF	Yes [48,102]	Yes [130]
M-CSF	Yes [95,103]	Yes [129]
GM-CSF	Yes [46]	Yes [126,129]
Synthesis of Chemokines		
Rantes (CCL5)	Yes [104,105]	Yes [129]
IP-10 (CXCL10)	Yes [105,106]	Yes [129]
Synthesis of Proteins Involved with Megakaryocyte Migration and Matrix Remodeling		
TIMP-1	Yes [107,108]	Yes [74,131]
MMP-9	Yes [109,110]	Yes [73,74]
Synthesis of Proteins Involved with Bone Remodeling		
RANKL	Yes [111]	Yes [132]
Osteoprotegerin	Yes [111]	Yes [132]
Synthesis of Coagulation Proteins and Enzymes		
Fibrinogen	Yes [5]	Yes [32,133,134]
Urokinas Plasminogen Activator	Yes [46]	Yes [135]
Synthesis of Connective Tissue Protein		
Fibronectin	Yes [112]	Yes [133]
Synthesis of Prostaglandin Synthesizing Enzyme		
Cyclooxygenase-2	Yes [113,114]	Yes [136]
Synthesis of Other Enzymes		
A1 antitrypsin	Yes [5,28]	Yes [137]
Acid phosphatase	Yes [115]	Yes [32]

Abbreviations used in TABLE 3: AP-1 – activator protein – 1, ERK – extracellular signal regulated kinase 1/2, FGF2 – fibroblast growth factor 2, GM-CSF – granulocyte macrophage colony stimulating factor, IL – interleukin, Jak – Janus kinase, MAPK – mitogen activated protein kinase, M-CSF – macrophage colony stimulating factor, MEK – MAPK/ERK kinase, MMP -9 – matrix metalloproteinase 9, NFAT – 1 – nuclear factor of activated T cells, NF*k*B – nuclear factor necessary for immunoglobin kappa light chain transcription in B cells, PDGF – platelet derived growth factor, PI-3K – phosphatidyl – inositide 3 kinase, RANKL – receptor activator of nuclear factor *k*B ligand, STAT – signal transducer and activator of transcription, TGF- B - transforming growth factor B, TIMP-1 – tissue inhibitor of metalloproteinase 1, TNFα – tumor necrosis factor α, VEGF – vascular endothelial growth factor.

Even though the Hodgkin, R/S, Lacunar and Mummified morphologies were delineated some time ago, the relationship between them remains elusive. Anagnostou et al. [13] delineated four morphologies within the malignant cells of Hodgkin's Disease that they believed were components of a developmental sequence. The model outlined in this paper follows them in proposing that the presumptive malignant cells of HD form a developmental sequence, but differs in equating this sequence to that which occurs during the maturation of megakaryocytes (**TABLE 1**). The megakaryoblast, with its large, round [32] nucleus is the only cell in the megakaryocyte sequence to undergo endomitosis [33]. During this process the nuclear outline is smooth and the cytoplasm remains immature, consisting mainly of ribosomes and polyribosomes [17,33]. A smooth, round nuclear outline and immature cytoplasm also characterize the Hodgkin cell [13,14] and it, like the megakaryoblast, is the only cell in the HD lineage to undergo endomitosis [37,38]. When endomitosis ceases the megakaryoblast nucleus begins to segment into lobules [31,33], following the pattern seen in granulocytes, and the cytoplasm begins to mature. The Golgi apparatus starts to produce azurophilic granules and the demarcation membrane system (DMS) begins to form [32,33]. These same features, a segmented nucleus and active Golgi apparatus, characterize the R/S cell [13,29] and it has been proposed that the R/S nucleus forms via the convolution, twisting and separation of the Hodgkin cell nucleus [38]. The R/S cell also contains an unusual membrane feature suggestive of an early DMS (**TABLE 1**). In the megakaryocyte lineage nuclear deformation continues as the cell matures to a granular/proplatelet producing megakaryocyte. At this point the nucleus is highly lobular [32,33] and the cytoplasm is filled with granules [32], two features of the Lacunar cell in HD (**TABLE 1**). When a megakaryocyte reaches this stage it organizes polarized microtubules into arrays that force the cytoplasm outward into long, thin processes called proplatelets [39]. It is from these processes that platelets are released. Similar long, thin processes have been seen emerging from the presumptive malignant cells of HD [30]. In addition Restin, an abundant R/S cell protein, is equated to CLIP-170 [7], a protein that binds to growing microtubules [40]. Once all platelets are released from the megakaryocyte it is left with only a thin rim of cytoplasm around the nucleus. This "naked" nucleus is very similar to the Mummified cell in HD, a similarity also noted by Lorenzen et al. [16].

3.3. The presumptive malignant cells of HD are functionally similar to maturing megakaryocytes

Our knowledge of cells has grown beyond a description of physical features to an understanding of function incorporating surface receptors, signaling pathways and transcription factors (TF). A comparison of the internal functioning of H/RS cells and megakaryocytes reveals numerous shared features. These suggest that the similarity in physical appearance between H/RS cells and maturing megakaryocytes is not coincidental. When H/RS cells are described the receptors most frequently mentioned are those of the tumor necrosis family, CD30 and CD40; however, these cells possess numerous other receptors and many of these are also present on megakaryocytes (**TABLE 2**). Some, such as the receptors for IL-6, -11 and -13, transmit signals

TABLE 4A. Functional similarities between H/RS cells and megakaryoblasts.

Feature	H/RS Cells	Megakaryoblasts
Active TF		
NFkB	Yes [88-90,138]	Yes [121,122]
Synthesis of Antiapoptotic Proteins		
Bcl-xl	Yes [140,142]	Yes [80,145]
Bcl-2	Yes [56,140,143]	Yes [145]
c-IAP-2	Yes [56,144]	Yes [122]
Changes in cyclin proteins		
Increased levels of cyclin E	Yes [22-24]	Yes [26]
Increased levels of cyclin D3	Yes [23,25]	Yes [26,27]
Increased levels of cyclin B	Yes [22,24]	Yes [27]

Abbreviations: IAP -2 – inhibitor of apoptosis protein 2; NF*k*B – nuclear factor necessary for immunoglobin kappa light chain transcription in B cells.

TABLE 4B. Functional similarities between H/RS cells and relatively mature megakaryocytes.

Feature	H/RS Cells	Megakaryocytes
Active TFs		
NFAT-1	Yes [95]	Yes [124]
P53	Yes [62,96,97]	Yes [125]
p21	Yes [96,97]	Yes [26]
Synthesis of Apoptotic Proteins		
Bak	Yes [140]	Yes [78]
Fas ligand	Yes [58,146]	Yes [124,129]
Caspase 3	Yes [140,144]	Yes [122,147]
Synthesis of Proteins Involved with Proplatelet Formation		
PKC	Yes [94]	Yes [148]
MMP-9	Yes [109,110]	Yes [73,74]
Actin	Yes [93]	Yes [32,133,148]
Tubulin	Yes [93]	Yes [35]
$\alpha 5\beta 1$	Yes [52]	Yes [76]

Abbreviations: MMP-9 – matrix metalloproteinase 9; NFAT-1 – nuclear factor of activated T cells; PKC – protein kinase C.

critical for megakaryocyte growth and proliferation [63,65,66]. Others, such as c-kit, c-met and CXCR4, enable megakaryocytes to interact with stromal cells in the bone marrow [63,72-74].

The similarity between H/RS cells and megakaryocytes does not end with cell receptors but encompasses the next step, the signaling cascade. Three cascades, the MEK/ERK (a MAPK pathway) [61], JAK/STAT [84-86] and PI3K-Akt [87] are unusually active in H/RS cells. These same signaling pathways are also very active in megakaryocytes (**TABLE 3**), where they play an important role in differentiation and cell survival [73,116-120].

Signaling pathways activate specific TFs that, in turn, initiate the transcription of specific genes. Numerous TFs active in H/RS cells are also active in megakaryocytes and, as a result, these cells synthesize many of the same proteins (**TABLE 3**). Of all the TFs active in H/RS cells the one most closely associated with them is the nuclear factor necessary for immunoglobin kappa

light chain transcription in B cells (NFkB). Constitutive activation of this TF is a hallmark of H/RS cells [88,138]. It stimulates the transcription of numerous genes, some of which produce antiapoptotic proteins [94,138]. These proteins, such as Bcl-xL [138], c-Flip [59] and c-IAP2 [138], protect H/RS cells from apoptosis and are thought to contribute to their malignant character.

There is, however, another side to H/RS cells. In addition to NFkB, and its antiapoptotic activities, these cells transmit signals leading to death. Many of them possess the death receptors Fas (CD95) [56-60] and TRAIL [61]. In some, the Fas (CD95) death inducing system is actually up regulated [59]. H/RS cells also contain Bax [139], an apoptotic protein, and caspase 3 [140], an enzyme in the apoptotic pathway. Given these observations it is not surprising that the presumptive malignant cells of HD undergo apoptosis with an apoptotic index (percentage of apoptotic cells) ranging from 0 to 47% [60,141].

Transmission of both antiapoptotic and apoptotic signals is yet another characteristic shared by H/RS cells and megakaryocytes. As megakaryocytes mature they pass from an endomitotic stage, characterized by antiapoptotic signals (**TABLE 4A**), into a period of cytoplasmic maturation and proplatelet formation, characterized by apoptotic signals (**TABLE 4B**). One of the TFs active during megakaryocyte endomitosis is NFkB [121,122] (**TABLE 4A**), the hallmark of H/RS cells. Once megakaryocyte endomitosis ends the activity of this TF declines [116,122] while the activity of another, nuclear factor of activated T cells – 1 (NFAT-1), increases [124]. NFAT plays a role in the transcription of the Fas ligand [124], which activates the Fas (CD95) death receptor and apoptotic pathway. This same TF, NFAT-1, is present in H/RS cells [95], along with the Fas ligand and several proteins involved in proplatelet formation (**TABLE 4B**). During megakaryopoiesis proplatelet formation is followed by the release of platelets and apoptosis of the denuded megakaryocyte. The apoptotic index for megakaryocytes [36,149] is similar to that for R/S cells.

As noted above, both megakaryocytes and H/RS cells transmit antiapoptotic and apoptotic signals. In megakaryocytes it is understood that these signals are sequential with apoptotic signals replacing antiapoptotic signals as the cells mature. In H/RS cells the timing of these signals is not yet appreciated because the various cell morphologies are studied as a single population. As a result, cells with antiapoptotic [150] or apoptotic proteins [139] are found alongside cells that lack these proteins. One prediction of the proposed model is that as Hodgkin cells are equated to megakaryoblasts they should all express antiapoptotic proteins and as R/S and Lacunar cells are equated to more mature megakaryocytes they should all express apoptotic proteins.

4. Hodgkin's Tissue is Equated to Extramedullary Hematopoietic Tissue

4.1. Hodgkin's and extramedullary hematopoietic tissue have similar physical and cellular features

The numerous similarities between the presumptive malignant cells of HD and megakaryocytes suggest that Hodgkin, R/S, Lacunar and Mummified cells are equivalent to maturing megakaryocytes. This indicates that Hodgkin's tissue supports the differentiation of hematopoietic cells, that it is a site of extramedullary hematopoiesis. Physical similarities between Hodgkin's tissue and bone marrow support this assertion. In the nodular sclerosis form of HD orderly, interconnected bands of dense, laminar, relatively a-cellular collagen [1,2] subdivide the tissue into nodules, just as trabecular bone subdivides hematopoietic tissue of the marrow. The equivalence of this collagen and bone is further supported by the presence of spherical calcified bodies in Hodgkin's tissue [151].

If Hodgkin's tissue is a site of hematopoiesis H/RS cells are not surrounded by a reactive, inflammatory infiltrate but by other maturing

hematopoietic cells in a stromal framework. The cells comprising Hodgkin's tissue support this prediction as they consist of numerous lymphocytes, some of which may be progenitor cells, and cells at various stages of maturation, such as myelocytes [152,153] and granulocytes [152]. Erythroblasts may also be present as both iron [154] and ferritin [155] occur in Hodgkin's tissue. This tissue also contains numerous fibroblast-like and interdigitating reticular cells that play the role of a supportive stromal network. Their cytoplasmic projections envelope H/RS cells [51] just as those from marrow stromal cells encompass primitive hematopoietic cells [156] and like marrow stromal cells [157,158,159] they synthesize stem cell factor [51], hepatocyte growth factor [52] and stromal derived growth factor-1 [53]. Endothelial cells in Hodgkin's tissue also support its hematopoietic character as they express vascular cell adhesion molecule -1 [160] and E selectin [161], proteins synthesized by endothelial cells located in hematopoietic tissue [162].

Another similarity between marrow and Hodgkin's tissue involves T lymphocytes. They appear to play a role in the development of both megakaryocytes and H/RS cells. Conditioned media from a T cell line increased the number and size of megakaryocyte colonies [163], while activated T lymphocytes augmented proliferation of CFU-Meg in culture [164]. Similarly, H/RS cells are frequently surrounded by T lymphocytes [30]. These rosetting lymphocytes are not responsive to mitogen or antigen [165], but they express CD40L [166], which interacts with the CD40 receptor on H/RS cells [166]. Just as signals from T lymphocytes appear to stimulate proliferation of megakaryocytes, signals from T lymphocytes may stimulate growth of H/RS cells [166].

Finally, the equation of Hodgkin's and extramedullary hematopoietic tissue helps explain one of the most unusual characteristics of HD, the rarity of the presumptive malignant cells. Almost every paper on the topic notes that H/RS cells comprise less than 1% of the cells in Hodgkin's tissue [167]. Once the equivalence of Hodgkin's and hematopoietic tissue is appreciated this rarity is to be expected as megakaryocytes comprise only .03 to .06% of nucleated cells in bone marrow [168].

4.2. Hodgkin's and extramedullary hematopoietic tissue occur in similar sites throughout the body

Hodgkin's tissue not only physically resembles extramedullary hematopoietic tissue, it also occurs in similar sites throughout the body. Although HD is frequently assumed to be restricted to lymph nodes, this is not the case. Some of the other organs in which it occurs include the spleen, liver, GI tract, pancreas, adrenal glands, kidney, uterus, ovaries, breast, bladder, lungs and heart [153,169], all of which are also sites of extramedullary hematopoiesis [170].

5. Hodgkin's Tissue in Bone Marrow is Equated to Myelofibrosis

As noted above, Hodgkin's tissue can appear in almost any organ of the body. The proposed model equates these occurrences to extramedullary hematopoiesis with one exception, when it occurs in the bone marrow. In this location Hodgkin's tissue is described as a highly fibrotic lesion composed of lymphocytes, histiocytes, plasma cells and large cells with hyper segmented nuclei [171]. The similarity between these lesions and those that occur in myelofibrosis [172] suggests that HD in bone marrow is actually a fibrotic process.

5.1. Impact of marrow damage in HD

Although Hodgkin's tissue in the marrow is restricted to these fibrotic lesions marrow damage is not. A detailed study of supposedly normal marrow in HD revealed scattered foci of fibrosis, increased inflammatory infiltrate, focal or massive oedema, necrosis of capillaries and arterioles, and disturbed hematopoietic architecture [173]. The severity of this marrow damage ap-

pears to increase with disease progression as there is a direct correlation between the extent of erythropoietic disturbance in the marrow and stage of the disease [173]. The impact of marrow damage is also reflected in the blood as patients progress from a mild normochromic, normocytic anemia in the initial stages of the disease to more severe anemia in later stages [153,169]. One study suggests that this anemia is the result of impaired incorporation of iron into circulating erythrocytes [174]. The same type of deterioration occurs in the white blood cells as relatively normal counts in initial stages of the disease become abnormally high in later stages [153]. This may reflect the accumulation in the blood of immature granulocytes [33], as immaturity decreases cell deformability, mobility and adhesion [175], which slows cell exit from the vascular system [175]. Of all the blood elements only platelets are significantly increased in the early stages of the disease [153].

5.2. Possible cause of myelofibrosis

The cause of the myelofibrosis that accompanies HD is currently unknown, but some evidence suggests it may be the result of a damaging increase in marrow pressure triggered by an elevation in blood volume. A similar idea was proposed by Schiel [176] for the myelofibrosis that accompanies carcinoma. HD patients frequently have an expanded plasma volume [174]. Additional evidence of abnormally high blood flow can be found in the blood vessels of these patients as they display an unusual flattened shape attributed to a decrease in intraluminal pressure and increase in blood flow [177]. An elevated blood volume would increase strain on endothelial cells, and their intercellular junctions, which could explain why endothelial cells in HD patients release tissue factor [161], an initiator of the coagulation protein cascade. An increased strain on intracellular junctions could also explain the thrombocytosis that occurs early in HD as platelets release growth factors that help maintain tight endothelial junctions [178].

6. Conclusion

Current medical thinking attributes H and R/S cells to the genetic mutation of a cell that normally resides in the lymph node. The numerous similarities between H/RS cells and megakaryocytes do not support this theory but instead suggest that H/RS cells are maturing megakaryocytes. Considered on its own, and not as a competitor to a long held hypothesis, the idea that H/RS cells are immature megakaryocytes residing in extramedullary hematopoietic tissue is plausible. Given the potential implications for the treatment of HD it should be experimentally tested.

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