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Invited Review

The hemopoietic system: a phylogenetic approach

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Summary. Nomadism is a true hemopoietic characteristic during vertebrate phylogeny and ontogeny.

This work reviews the mechanisms and developmental steps of hemopoiesis, from a phylogenetic point of view. A summary of the principal hemopoietic «foci» along the evolutionary line is also presented.

Key words: Hemopoiesis, Phylogeny

Introduction

All biological systems tend to reach the maximum possible size. When the surface:volume ratio of protists became inadequate for metabolite exchange, multicellularity was adopted to achieve the maximum energetic efficiency and size. The acquisition of one or more simple cavities allowed the development of multiple forms in spite of the absence of a specialized system for distribution and disposal of metabolites. The development of a circulatory system provided a new approach for the energetic problem. Likewise, as biological complexity increases, multiple cellular subsystems appear, each one associated with a specific function such as oxygen transport, blood clotting or immune response (Glomski and Tamburlin, 1990).

In most simple forms, metabolites are transported in solution through an acellular fluid (Glomski and Tamburlin, 1989). "Lower" invertebrates lack hemopoiesis, probably because their short life time fits well with the time course of blood cells (Tavassoli, 1991). Most plathelmints and nematods present occasional mitosis in their hemocytes (intravascular hemopoiesis) (Sminia, 1974), while true coelomate have vascularized aggregates of hemopoietic cells behind vascular or visceral walls (extravascular hemopoiesis) (Andrew, 1965; Glomski and Tamburlin, 1990).

General phylogeny of hemopoiesis

As general rule, hemopoiesis is, from the beginning, a «*nomadimic*» mesoderm-associated process (Tavassoli, 1991): its development as a blood cell producing system shows many "experiments of nature" (Aggio, 1987) along the phylogenetic line until its final settlement in specific organs, underscoring the importance of studying «lower» species as a complementary method for a better knowledge of the mechanisms involved in «higher» groups (Tavassoli, 1986).

Hemopoietic organs are clusters of developing cells, all of them derived from a unique precursor (stem cell) and framed in a hemopoietic stroma or "microenvironment" (Owen, 1988) which has been characterized only partially in mammals (Gordon, 1988; Tavassoli and Minguell, 1991), while data from lower species are rare (Castillo et al., 1990; Gallego et al., 1995; Zapata, et al., 1995).

Hemopoiesis consists basically in the conversion of pluripotent progenitors the into functionally, highly specialized cells, frequently destined to live for a few hours or weeks before being sequestered, destroyed and replaced. Hemopoiesis has been classically separated into lymphopoiesis (producing lymphocytes and plasma cells), and myelopoiesis (resulting in platelets, erythrocytes, granulocytes and monocytes).

In ectothermic vertebrates, lymphopoiesis and myelopoiesis are anatomically associated. Permanent separation between these tissues is first seen in birds, when lymph node and bursa of Fabricius become well defined structures (Cohen and Siegel, 1982). In mammals, this separating process takes place during the fetal life when lymphatic organs (spleen, lymph nodes) are fully functional and myelopoiesis settles exclusively and permanently in the bone marrow. It is interesting to note that there are multiple remaining examples of simultaneous splenic and bone marrow myelopoiesis in adult rodents (Fruhman, 1970; Hayes, 1973), insectivores (Fukuta et al., 1982; Tanaka, 1986b), edentates (Weiss and Wislocki, 1956; Hayes, 1970) and monotrems (Tanaka, 1986a; Tanaka et al., 1988).

Basic hemopoietic mechanisms in vertebrates.

Along their path towards differentiation, hemopoietic precursors are influenced by several factors which guide them through the following developmental, irreversible

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steps: migration, nidation, commitment, proliferation, differentiation and a final functional phase which in turn is followed by death either by programmed senescence (apoptosis) (Cowling and Dexter, 1994) or at random (Necas et al., 1993). Emergence from the system is compensated by an identical imput of cells, a delicate equilibrium kept through precise feedback mechanisms.

Migration until settlement in the appropiate organ is supported by a circulating pool of stem cells, responsible for the nomadism observed not only in phylogeny but also during ontogeny (Nicolas-Bolnet et al., 1991), as remarked below.

Nidation, commitment, and proliferation of hemopoietic cells are influenced not only by their immediate microenvironment and their products: cytokines (interleukins and hemopoietic growth factors) (Zipori, 1992, Bronchud, 1995), and "homing molecules" (Abboud et al., 1994) but also by specific "long range" hormones (such as erythropoietin) (Zipori et al., 1985), contact cell-to-cell influences, and the surrounding microvasculature (Zipori, 1988). The presence of special receptors present in the cell surface at each stage of development is also essential (Metcalf, 1993). It is probable that some or many of these ways of directing stem cells until their final destination are common to all vertebrates, since their end products are very similar (Rosse and Waldman, 1966; Zanjani et al., 1969).

These mechanisms are permanently operative in endothermics, while ectothermics show marked seasonal variations (Zapata et al., 1992; Siegl et al., 1993), probably as adaptative strategies to meet environmental and metabolic requirements.

Hemopoietic «*foci*» and circulating cells in vertebrates

Circulating cells of vertebrates are classically divided into five main types: lymphocytes, monocytes/macrophages, erythrocytes, thrombocytes/platelets and granulocytes.

Lymphocytes and macrophages are quite homogeneous along the group and some observations have even suggested the existence, in "lower" vertebrates, of subgroups similar to those seen in man (Tomonaga et al., 1985; Evans and Cooper, 1990).

Erythrocytes are anucleated in mammals or nucleated in others vertebrates. Comparative data show a well-defined inverse relationship between cell size and

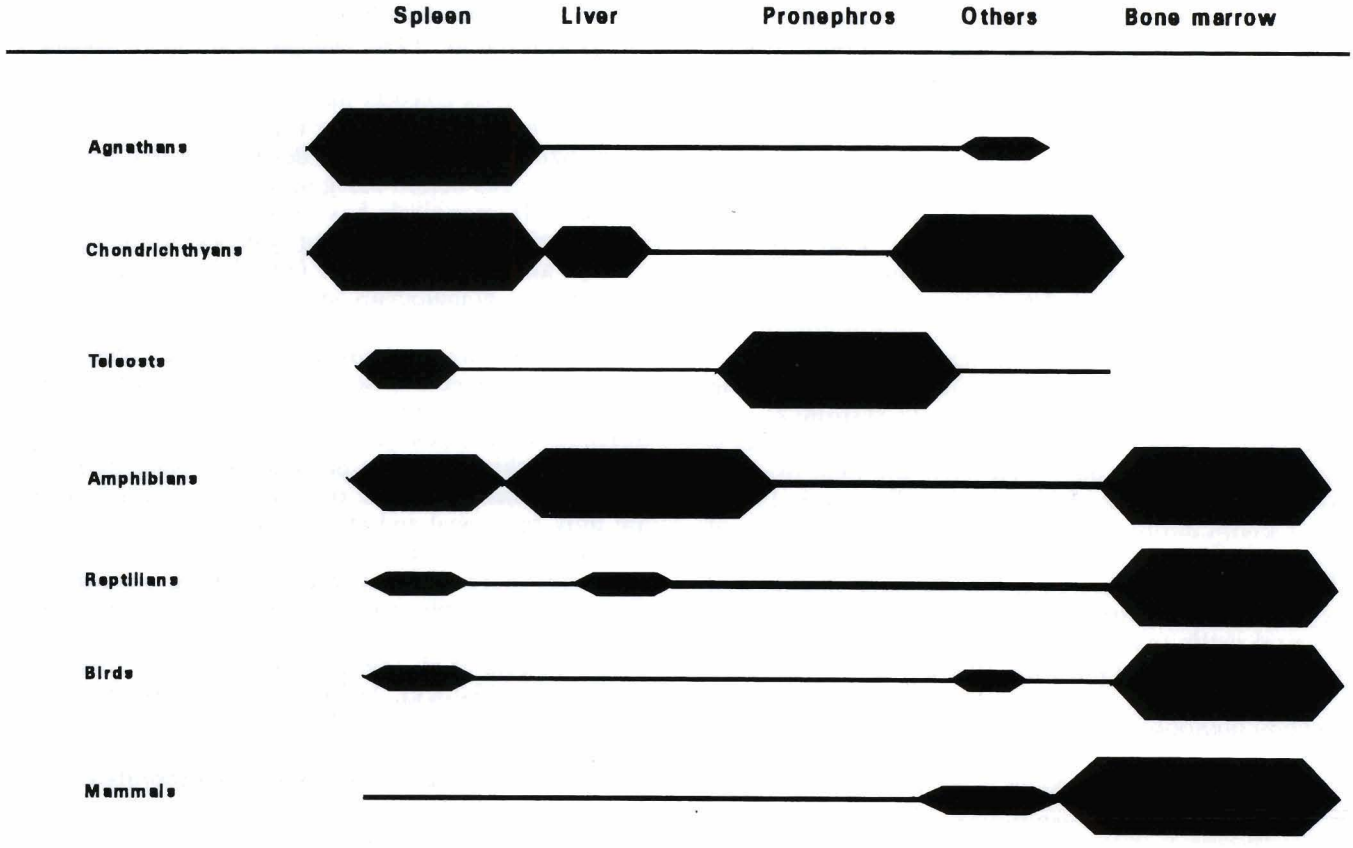

Fig. 1. Principal hemopoietic-foci in vertebrate phylogeny. Size of trapezes is according to the importance of the organ in the hemopoiesis.

circulating number (Fänge, 1984).

Thrombocytes and granulocytes show marked diversity. The former are polymorphous cells complete or anucleated, and little is known about their developmental stages in non mammalian species (Daimon et al., 1977; Pica et al., 1990). They are linked with coagulation and hemostasis from chondrichthyans (Daimon and Uchida, 1985; Pica et al., 1990).

Granulocytes are heterogeneous cells with confusing terminology and functions still obscure. Generally, they pertain to the acidophylic, neutrophylic and basophylic lines, with morphological intraspecies variations (Andrew, 1965).

Hemopoietic «foci» are ubiquitous (Fig. 1). Agnathes concentrate their hemopoietic functions in a diffuse gut-associated tissue, probably homologous to the spleen of more advanced organisms (Zapata, 1983). Cartilaginous fishes direct granulopoiesis to specific places such as Leydig's organ (in the submucosa of the oesophagus) and the epigonal organ (Galíndez, 1994). Teleosts bear the most important "foci" in their pronephros (Fänge, 1984). In amphibians, the bone marrow (supplemented by the spleen) takes place as the rector organ of hemopoiesis. All these variations suggests that in absence of the bone marrow several mesodermic tissues are used for homing hematopoiesis. The emergence of rigid bones (together with terrestrial life) is followed by the emigration of hemopoietic cells to the marrow. The adaptative significance of this event is unclear, although it could have been related to the adoption of a more protected environment for an indispensable function (Tavassoli, 1986).

Ontogeny of hemopoiesis in vertebrates

Embryonic and fetal hemopoiesis is also a migratory phenomenon. A typical example is provided by the mouse, in which primitive hemopoietic cells appear first in the yolk sac (Moore and Metcalf, 1970) to later migrate and colonize in the liver and spleen and then to the bone marrow in a final transfer. At each step, the respective microenvironment should obviously be prepared to receive them by offering the appropiate seedbed for proliferation and differentiation (Migliacchio et al., 1976). This migratory pattern is also observed in very distant groups such as fishes (Teshima and Tomonaga, 1986; Doggett and Harris, 1987) and birds (Dieterlen-Lièvre, 1994) although in these animals the the final localizations are quite variable.

The hemopoietic «*foci*» that are operative during the whole life span of «lower» vertebrates are equal to those present in the embryonic and fetal stages of "higher" species. So the basic ontogenetic mechanisms must be present along all the phylogenetic line: that is to say that hemopoietic is basically supported by primitive cells genetically programmed to move and lodge in different organs, which in turn are also genetically programmed to offer the appropriate environment in due time.

Final comment

Hemopoiesis is an old process whose origin is concomitant or subsequent with the coelom. In physiological conditions, it requires an appropriate «niche» and a complex system of regulatory influences located in the cellular microenvironment or coming from distant sources, interacting with specific receptors present in the surface of the hemopoietic cells.

In vertebrates, hemopoiesis runs a long way, starting in the yolk sac and ending in the bone marrow and lymphatic structures, having passed through the liver, the spleen and other tissues that are circumstantially or permanently active.

Evolutionary aspects are not sufficiently studied, and since the cellular environment exerts a crucial influence on the differentiation of hemopoietic stem cells, the spontaneous models offered by «lower» vertebrates with their «dissected» loci may offer an original approach to better understand the basic mechanisms involved.

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