

# Scavenger endothelial cells of fish, a review

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## Abstract

The definition of scavenger endothelial cells (SEC) is exclusively based on functional and structural characteristics. The following characteristics are common hallmarks for the vertebrate SEC: (a) All vertebrates examined are furnished with a population of special SEC that plays a role in the catabolism of physiologic and non-physiologic soluble waste macromolecules. (b) From the ligands that are endocytosed, SEC in all seven vertebrate classes appear to express the collagen  $\alpha$ -chain receptor and the scavenger receptors. In addition, the hyaluronan and the mannose receptors are present on SEC of mammalia (several species) and osteichthyes (e.g., salmon and cod). It is likely that all four receptor types are present in all vertebrate classes. (c) Like liver endothelial cells (LEC) in mammals, SEC in all vertebrate classes are geared to endocytosis of soluble macromolecules, but phagocytic uptake of particles is taken care of mainly by macrophages. (d) The most primitive vertebrates (hagfish, lamprey and ray) carry their SEC in gill vessels, whereas phylogenetically younger fishes (salmon, carp, cod and plaice) carry their SEC in either kidney or heart and in all terrestrial vertebrates—SEC are found exclusively in the liver. (e) SEC of all vertebrates are localized in blood sinusoids or trabeculae that carry large amounts of slowly flowing and O<sub>2</sub> poor blood. (f) SEC differs functionally and structurally from what is normally associated with “conventional vascular endothelium.”

## KEYWORDS

endocytosis, endothelium, fish, scavenger receptor, teleost

## 1 | INTRODUCTION

### 1.1 | Non-phagocytic and phagocytic scavenger cells in lower vertebrates

The vertebrates (Figure 1) are a subphylum of the chordata, characterized by the possession of a brain enclosed in a skull, ears, kidney and other organs. In most vertebrates, a well-formed bony or cartilaginous vertebral column or backbone is enclosing the spinal cord (Lawrence, 1997).

Fish constitute more than one-half of the total number of approximately 48,000 recognized vertebrate species living today. The teleosts (modern bony fishes) represent the majority. The remainders are elasmobranch (sharks and rays, approximately 700 species) and about 170 other species (Nelson, 1994). Studies in fish, amphibians and reptiles have recently revealed that even these vertebrates carry a specialized endothelium that carry out a scavenger function corresponding to that of the rat liver endothelial cells (Seternes et al., 2002). An overview over the anatomical distribution of soluble markers and the presence of scavenger endothelial cells in different fish is presented in Table 1.

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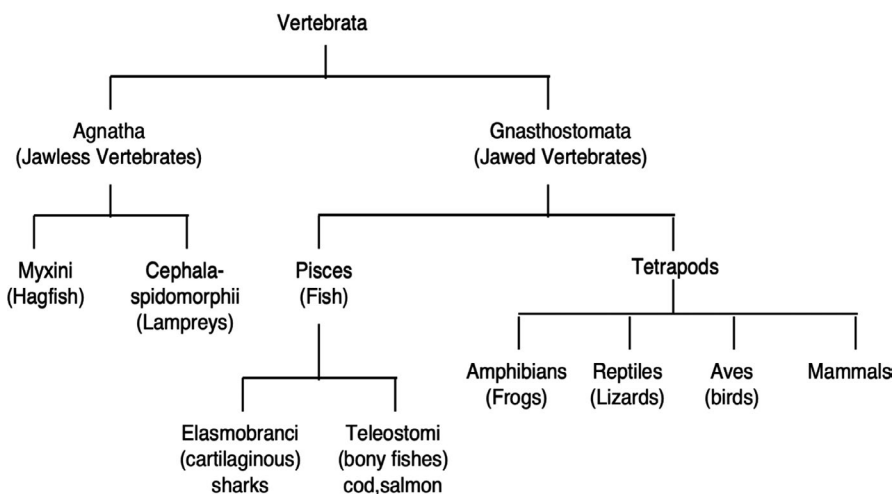
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## 1.2 | Phagocytic and non-phagocytic cells in vertebrates

Today, the various mechanisms used by cells for internalization of fluids, macromolecules and particles are collectively termed endocytosis. Endocytosis is common to all mammalian cells and serves a wide variety of functions including synaptic transmission growth control, degradation of extracellular material and antigen processing. In addition, it mediates the entry of many opportunistic pathogens, such as viruses and toxins (Mukherjee et al., 1997). Depending on the material internalized and the mechanisms involved in internalization, endocytosis can be divided into two main types: phagocytosis ("cell eating") and pinocytosis ("cell drinking") (Silverstein et al., 1977). Phagocytosis is the internalization of larger particles (>0.5  $\mu\text{m}$ ) like bacteria and senescent cells and normally occurs in professional phagocytes (such as macrophages and granulocytes), where the cytoskeleton is actively involved in the internalization process (Swanson & Watts, 1995). Pinocytosis refers to the constitutive formation of vesicles containing extracellular fluid and macromolecules specifically or non-specifically bound to the plasma membrane. This process is carried out in one or more forms by all eukaryotic cells (Mellman, 1996). The common feature of both pinocytosis and phagocytosis is the apparent involvement of the actin cytoskeleton (Riezman et al., 1997). Pinocytosis is further divided into fluid-phase endocytosis of bulk solutes and receptor-mediated endocytosis, where macromolecules are concentrated before internalization due to their receptor binding. Some authors use the term endocytosis synonymously with pinocytosis. Receptor-mediated endocytosis is the best-characterized process, and its hallmark is clathrin-dependent internalization from the plasma membrane (reviewed by Hubbard, 1989). Different mechanisms, not dependent on clathrin, have also been described as internalization pathways. These are clathrin-independent endocytosis, macropinocytosis and uptake via caveolae (reviewed in Anderson et al., 1992). Phagocytosis is a complex cellular event by which larger particles are recognized, engulfed and eliminated by specialized cells (macrophages/granulocytes). The recognition of particles/pathogens/apoptotic cells involves engagement of pathogen-associated molecular patterns

(PAMPs) by pattern recognition receptors (PRR) on the phagocyte (Franc et al., 1999). This recognition step results in both the movement of phagocyte membrane (guided by the actin cytoskeleton) around the target and the formation of the phagosome. The nascent phagosome then traverses the cell and usually fuses with a lysosome, where the contents of the phagolysosome are digested by hydrolytic enzymes (Beron et al., 1995; Silverstein et al., 1977).

Kupffer cells constitute 80%–90% of total fixed macrophages in the body of mammals (Phillips, 1989). They generally reside within the lumen of the liver sinusoids, adherent to the endothelial lining, partially obscuring the vascular channel morphology (Tamaru & Fujita, 1978; Wisse, 1977). Kupffer cells are found in the hepatic sinusoids in vertebrates ranging from amphibians to mammals but not in fish (Awaya, 1983; Speilberg et al., 1994). Kupffer cells are found in greatest number in the periportal area and, therefore, constitute the first macrophage population that comes in contact with bacteria and bacterial products such as endotoxin transported from the gut to the liver (Fox et al., 1987). Consequently, Kupffer cells are constantly exposed to factors known to activate macrophages (Gregory & Wing, 1998). Kupffer cells comprise the clearance and elimination of bacterial pathogens from the bloodstream in a three-staged model: (a) The majority of bacteria that enter the bloodstream are trapped in the liver and bound to the surface of Kupffer cells; (b) Kupffer cells stimulated by infection express cell adhesion molecules and produce cytokines, chemokines and other soluble proinflammatory factors that promote the influx, localization and biological activity of neutrophils; and (c) infiltrating neutrophils kill the extracellular bacteria associated with Kupffer cells, secrete soluble factors that enhance the inflammatory process and promote the resistance and/or antimicrobial activity of other cell populations of the liver. Kupffer cells are generally considered fixed tissue macrophages of the liver. However, high-resolution *in vivo* video microscopy has demonstrated that Kupffer cells have the ability to migrate along sinusoidal walls and that they are able to arrest the blood flow in an individual sinusoid by partially blocking (MacPhee et al., 1995; Wisse, 1970). By reducing the blood flow in the sinusoid, the Kupffer cells enable formation of contact between leukocytes and cells (antigen-presenting cells) of the hepatic sinusoid.



**FIGURE 1** General scheme of classification (phylogenetic) of the major groups of vertebrates

**TABLE 1** Anatomical distribution of soluble ligands and markers of the scavenger endothelial cells in different fish

Fish species	Tissues	Ligand	References
<i>Cl. Agnatha</i>			
Hagfish	Gills	Sepia ink	Tomonaga et al. (1975)
Lamprey ( <i>Lampetra fluviatilis</i> )	Gills	Colloidal carbon	Page and Rowley (1984)
<i>Cl. Chondrichthyes</i>			
Dogfish ( <i>Squalus acanthias</i> )	Gills	India ink	Kempton (1969)
Dogfish ( <i>Scyliorhinus canicula</i> )	Gills, peripheral blood	Colloidal carbon latex beads, sheep red blood cells, bacteria, dextran	Hunt and Rowley (1986)
<i>Cl. Osteichthyes</i>			
Cunner ( <i>Tautoglabrus adspersus</i> )	Heart	Colloidal carbon	Mackmull and Michels (1932)
Plaice ( <i>Pleuronectes platessa</i> )	Heart	Colloidal carbon, yeast, Salmonella gallinarum	Ferguson (1975)
Plaice ( <i>Pleuronectes platessa</i> )	Spleen, kidney, heart	Particulate material	Ellis et al. (1976)
Char ( <i>Salvelinus alpinus</i> )	Kidney	Denatured serum albumin	Dannevig and Berg (1978)
Char ( <i>Salvelinus alpinus</i> )	Kidney, liver	Denatured serum albumin, mannose-terminated glycoprotein	Smedsrod et al. (1984)
Rainbow trout ( <i>Oncorhynchus mykiss</i> )	Kidney	<i>Salmonella pullorum</i>	Ferguson (1984)
Rainbow trout	Head kidney	Ovalbumin, dinitrophenylated human serum albumin	Dannevig et al. (1994)
Rainbow trout	Kidney	<sup>51</sup> Cr-labelled heat-killed <i>Salmonella pullorum</i>	Ferguson et al. (1982)
Rainbow trout	Pronephros cells	DNP-HSA, formaldehyde-treated HSA, invertase	Dannevig et al. (1990)
Rainbow trout	Kidney, liver	High-density lipoprotein	Gjoen and Berg (1992a, 1992b)
Rainbow trout	Kidney, liver	LDL	Gjoen and Berg (1993)
Rainbow trout	Pronephros cells	Chemically modified protein	Dannevig and Berg (1978)
Atlantic salmon ( <i>Salmo salar</i> )	Kidney, spleen	Lipopolysaccharide	Dalmo and Bøgwald (1996)
Atlantic salmon	Kidney	Collagen	Smedsrod et al. (1993)
Atlantic salmon	Kidney, spleen	LPS, A protein	Stensvag, Arnesan, et al. (1999)
Atlantic salmon	Kidney	LPS, A protein	Stensvag, Bogwald, et al. (1999)
Atlantic salmon	Head kidney, spleen	Extracellular products	Espenes et al. (1996)
Atlantic salmon	Kidney sinusoidal cells	Plasmid DNA	Tonheim et al. (2008)
Atlantic cod ( <i>Gadus morhua</i> )	Endocard	Collagen	Smedsrod et al. (1995)
Atlantic cod	Endocardial endothelial cells	Hyaluronan	Sorensen et al. (1997)
Atlantic cod	Endocardial endothelial cells	<sup>125</sup> I-TC-FSA, <sup>125</sup> I-PINP	Sorensen et al. (1998)
Atlantic cod	Heart, spleen, kidney	Laminaran	Dalmo et al. (1996)
Atlantic cod	Heart	Hyaluronan, chondroitin sulphate	Seternes, Oynebraten, et al. (2001)
Atlantic cod		<i>Vibrio salmonicida</i> LPS	Seternes, Dalmo, et al. (2001)
Atlantic cod	Liver, heart	<sup>125</sup> I- $\alpha$ -mannosidase, <sup>125</sup> I-TC-invertase, <sup>125</sup> I-asialo-orosomucoid	Sorensen et al. (2001)
Atlantic cod	Endocardial endothelial cells	Plasmid DNA	Seternes et al. (2007)
Atlantic cod	Heart, spleen, kidney	FITC-LPS	Dalmo et al. (1998)

(Continues)

TABLE 1 (Continued)

Fish species	Tissues	Ligand	References
Atlantic halibut	Heart, spleen, kidney	FITC-LPS	Dalmo et al. (1998)
Turbot	Kidney, spleen, liver	FITC-LPS	Dalmo et al. (1998)
Atlantic salmon, Atlantic cod	Endocardial endothelial cells	FITC-collagen	Koren et al. (1997)
Pearl gourami ( <i>Trichogaster leerii</i> )	Heart	Ferritin	Leknes (2007)
Platyfish ( <i>Xiphophorus maculatus</i> )	Heart	Ferritin	Leknes (2001, 2007a, 2007b, 2016)
Firemouth cichlid ( <i>Thorichthys meeki</i> )	Heart	Ferritin	Leknes (2009, 2011, 2016)
Buenos Aires tetra ( <i>Hyphessobrycon anisitsi</i> )	Kidney, spleen	Ferritin	Leknes (2012)
Firemouth cichlid ( <i>Cichlasoma meeki</i> )	Endocardium	Horse spleen ferritin	Leknes (1987)
Bronze cory ( <i>Corydoras aeneus</i> )	Endocardium	Horse spleen ferritin	Leknes (1987)
Medaka ( <i>Oryzias latipes</i> ) Goldfish ( <i>Carassius auratus</i> ) Lemon tetra ( <i>Hyphessobrycon pulchripinnis</i> )	Heart	India ink	Nakamura and Shimozawa (1994)

In the early 1970s, important electron microscopic studies, largely performed by Wisse, demonstrated that the liver endothelial cell (LEC) represents a separate cell type of the liver sinusoids (Wisse, 1970, 1972). These LECs, that form the continuous lining of the liver sinusoids, differ from other vascular endothelial cells in several aspects: (a) LEC lacks a continuous basement membrane. (b) Factor VIII-related (or von Willebrand factor) antigen (VIII:Ag), that is routinely used as a specific immunohistochemical marker of extrasinusoidal endothelial cells, is not expressed by LEC (at least not in rat). Rather, LECs have been reported to synthesize procoagulant factor VIII (Hellman et al., 1989). (c) The long cytoplasmic processes of LEC contain abundant pores or fenestrae with a mean diameter of approximately 100 nm that are arranged in so-called sieve plates. The total area of the fenestrae accounts for approximately 10% of entire surface of the LEC (Wisse, 1970; Wisse et al., 1983, 1985). (d) Wisse also described the presence in LEC of numerous coated pits and vesicles and large amounts of other organelles associated with endocytosis. In fact, LECs, which make up only 2.8% of the total liver volume, contain about 15% of the total lysosomal volume and approximately 45% of the pinocytotic vesicle volume of the liver (Blouin et al., 1977). Also, the specific activities of several lysosomal enzymes are higher in LEC than in other liver cells (Knook & Sleyster, 1980; Roden et al., 1989). Numerous studies investigating receptor-mediated uptake of macromolecules in the liver have clearly shown that even protein-coated gold particles as small as 15 nm do not pass freely through the fenestrae of LEC to reach hepatocytes (Kolb-Bachofen et al., 1984). Following i.v. injections, gold particles were observed only on the luminal (sinusoidal) side of the LEC; they were never detected in the Disse spaces or on the luminal side of hepatocytes (Kempka & Kolb-Bachofen, 1988). This means that LEC function as a barrier between macromolecules or leukocytes present in the sinusoidal lumen and hepatocytes (Fraser et al., 1995). LECs are also known to express a set of high-affinity

endocytic receptors for soluble macromolecular waste products, produced and released during normal tissue turnover, blood clotting, inflammatory processes and neoplastic development, which may be harmful if allowed to accumulate (Smetsrod et al., 1994).

Over the last decades, several studies have shown that sinusoidal LECs are uniquely endowed with the capacity to clear the blood from a number of physiological and foreign waste macromolecules. Most of these studies were performed with rat LEC and a few with LEC from other mammalian species. Similar studies in fish revealed that even these lower vertebrates carry a system of special scavenger endothelial cells. With the purpose to establish if these mammalian and fish scavenger endothelial cells represent a general vertebrate scavenger, or reticuloendothelial cell type, we set out to compare the anatomical and cellular site(s) of uptake of selected physiological and foreign soluble macromolecular waste substances in animal species from different vertebrate classes. The scavenger endothelial function of vertebrate species was presented in Seternes et al. (2002). All seven principal vertebrate classes were investigated: Mammalia (rat, mouse, pig); Aves (chicken); Reptilia (corn snake), Amphibia (frog); Osteichthyes, or bony fishes (plaice, cod, salmon, carp); Chondrichthyes, or cartilaginous fishes (ray); and Agnatha, or jawless fishes (lamprey and hagfish). The findings can be summarized as follows: The test ligands were taken up in the liver of all four classes of terrestrial vertebrates (Mammalia, Aves, Reptilia, Amphibia) in sinusoidal cells that are strikingly similar to mammalian LEC. In lower vertebrates, the test ligands distributed as follows: Osteichthyes: both endocardial and kidney sinusoidal endothelial cells (plaice), heart (both chambers) endocardial endothelial cells (Atlantic cod), or kidney (trunk and head) sinusoidal endothelial cells (Atlantic salmon and carp); Chondrichthyes and Agnatha: gill artery endothelial cells (ray, lamprey and hagfish). Stained latex beads coinjected in some experiments with labelled soluble test ligands clearly distinguished phagocytic macrophages from endocytic scavenger

endothelial cells in both higher and lower vertebrates. These observations suggest the existence of a distinct vertebrate scavenger endothelial cell system. Taken together, our results suggest that the endocytically active LECs of mammalia represent a special scavenger type of endothelium that has been conserved functionally throughout the evolution of the vertebrates (at least 500 million years). Our findings strongly motivate that the definition of the reticuloendothelial system of vertebrates includes both SEC, that eliminate soluble waste macromolecules from the circulation and macrophages that remove particulate material.

### 1.2.1 | Scavenger cells in the gills of Agnaths

The most ancient present living vertebrate is the primitive agnaths or jawless fish. This vertebrate superclass arose in the sea more than 500 million years ago and is today represented by two living families, the hagfish (myxiniids) and the lampreys (petromyzonids). The hagfish and lamprey are probably phylogenetically distant to each other. The high-walled endothelium lining the afferent branchial arterioles (*arteriae radiatae*) of the hagfish gills is characterized by having many micropinocytic vesicles and many electron-dense bodies dispersed in the cytoplasm (Kiyono, 1914). Distribution studies in inshore hagfish (*Eptatretus burger*) and black hagfish (*Paramyxine atami*) using horseradish peroxidase (ligand for mannose receptor) and sepia ink (ink from cuttlefish; between 100 and 260 nanometers in diameter) have demonstrated that these cells actively endocytose foreign material from the blood. Other cells which endocytose these substances in the hagfish are resident macrophages of the hepatic sinusoids (Tomonaga et al., 1975). The high-walled endothelial cells of the hagfish gills are also able to ingest latex beads and fixed blood cells (Tomonaga et al., 1973, 1979). The cavernous bodies of the lamprey gills contain specialized endothelial cells containing numerous vacuoles (Yamaguchi et al., 1978). The cavernous bodies form part of the blood vascular system and are located along the outer border of the axial plate of each gill filament. The body has a triangular shape in cross section and extends along the whole length of the filament. The afferent filament artery lies at the base of the cavernous body. Within the body are collagenous trabeculae that project into the blood lacuna. The blood lacunae are lined by two cell types, the cavernous body cells (CB cells) (Nakao, 1978) and a flat more conventional endothelial cell. The blood passes from the afferent filament through the cavernous body and thence to the gill lamellae and the efferent filament artery; in so doing, the blood is filtered by the cavernous body (Page & Rowley, 1984). Macrophages are also found in the lacuna, but they are readily distinguished from the lining cells (Yamaguchi et al., 1979). The CB cell is round or ovoid, about 50  $\mu\text{m}$  in diameter, and bulges into the lacuna. It is characterized by numerous pores on its surface and coated vesicles, phagosomes and residual bodies in the cytoplasm. As early as in 1933, it was demonstrated that the endothelial cells of the cavernous body are phagocytic (Gerard, 1933). Later studies showed that injected colloidal carbon, latex particles and fixed rat erythrocytes were

taken up by the CB cells as well as by the macrophages of the cavernous bodies in *Lampetra reissneri* and *Lampetra fluviatilis* (L.) (Page & Rowley, 1984; Yamaguchi et al., 1979). In contrast to the findings in hagfish, no resident phagocytes are found in the liver sinusoids of the lamprey (Kiyono, 1914).

### 1.2.2 | Scavenger cells in the gills of Elasmobranchs

Elasmobranchs, which include sharks, dogfish, rays and related forms, are fish with a long evolutionary history dating back some 400 million years. Injection of trypan blue and carmine into the dogfish resulted in accumulation of the dyes especially in the endothelium lining the arterial arches and large sinuses of the gills. Dyes were also found in the endothelium lining the splenic sinuses and hepatic sinusoids (Hoskins & Hoskins, 1918). There have been a number of reports of a cavernous body area existing in the elasmobranch gills (Kempton, 1969; Wright, 1973). Awaya et al. (1983), reported that the cartilaginous fishes (*Mustelus manazo*, *Raya kinojei* and *Dasyatis akajei*) are provided with CB structures in gills and that many of their lining cells (CB cells) are capable of phagocytosing foreign materials. The dogfish (*Scyliorhinus canicula*) CB cells contain three types of granular/vacuolar inclusions: (a) oval electron-dense homogenous granules which are probably lysosomes, (b) round electron-lucent bodies which sometimes contain a fluorescent material and (c) large oval-round which enclose peculiar rod-shaped crystalline inclusions (Hunt & Rowley, 1986). The CB cells probably perform a useful filtration function, as all blood entering the secondary lamellae has to first percolate through the phagocyte-lined lacuna of the CB. However, it has been pointed out that the pinocytic power of the CB cells is far more notable than their phagocytic capacity (Hunt & Rowley, 1986). It was also suggested that the main role of these cells may be the elimination of cell-breakdown products or microorganisms such as viruses from the circulation. Phagocytic cells probably homologous to mammalian Kupffer cells involved in phagocytosis of latex particles and carbon were described in the liver sinusoids of dogfish (Hunt & Rowley, 1986). Phagocytic cells were also observed in the ellipsoids and the red pulp of the spleen (Hunt & Rowley, 1986).

### 1.2.3 | Scavenger cells in teleosts

The teleosts or the bony fishes, with around 22,000 species, are almost as numerous, in terms of species, as all the other members of the vertebrate lineages put together. Organ uptake studies have revealed the kidney and spleen as being the main areas for phagocytic activity in teleosts. When radiolabelled bacteria are injected into rainbow trout, more than 70% of the radioactivity is found in the kidney (Ferguson et al., 1982). In the kidney, particles are initially internalized by phagocytic cells, while in the spleen material is trapped extracellularly on reticular fibres in the ellipsoid wall before internalization by phagocytic cells. Blood monocytes and tissue macrophages have been described as phagocytic cells in teleost

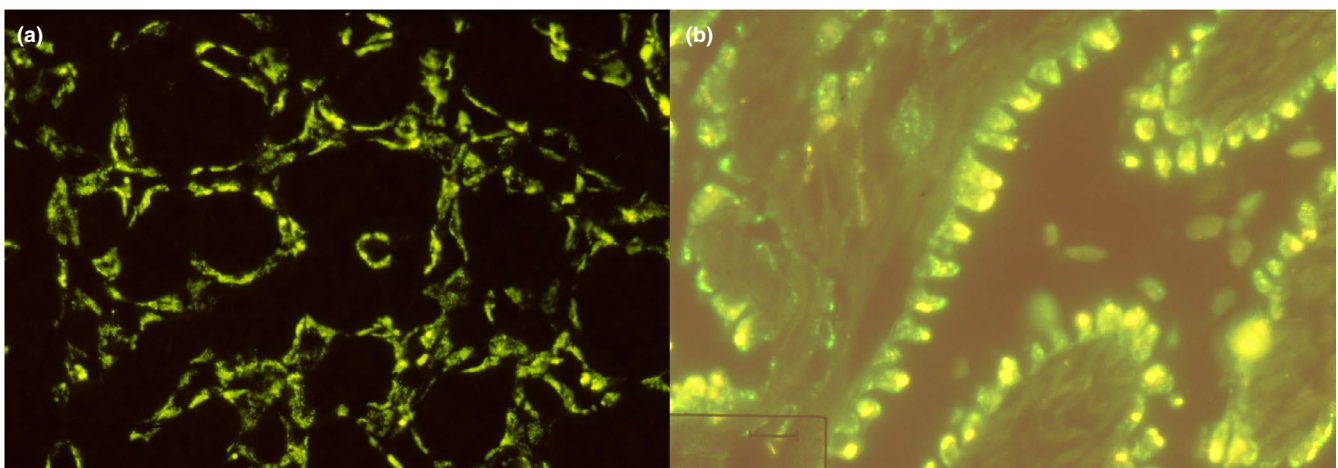


fishes (Dalmo et al., 1997; Lu & Chen, 2019; McKenney et al., 1977). Kiyono (1914) injected the vital stain lithium carmine into the body of the Striped catfish eel (*Plotosus lineatus*) and the Black cow tongue (*Paraplagusia japonica*) and found that the stain was taken up by endothelial cells in the kidney of the Striped catfish eel and in the heart endocardium of the Black cow tongue. Indian ink was injected into the peritoneal cavity of the cunner (*Tautoglabrus adspersus*), a marine teleost. The endothelial cells of the cunner heart were replete with carbon particles, in addition to phagocytic cells in the kidney and spleen (Mackmull & Michels, 1932). Similarly, colloidal carbon was found in the kidney, spleen and endocardial endothelial cells of the atrium of plaice (*Pleuronectes platessa*) (Ferguson, 1975).

#### *Sinusoidal endothelial cells in salmonid kidney*

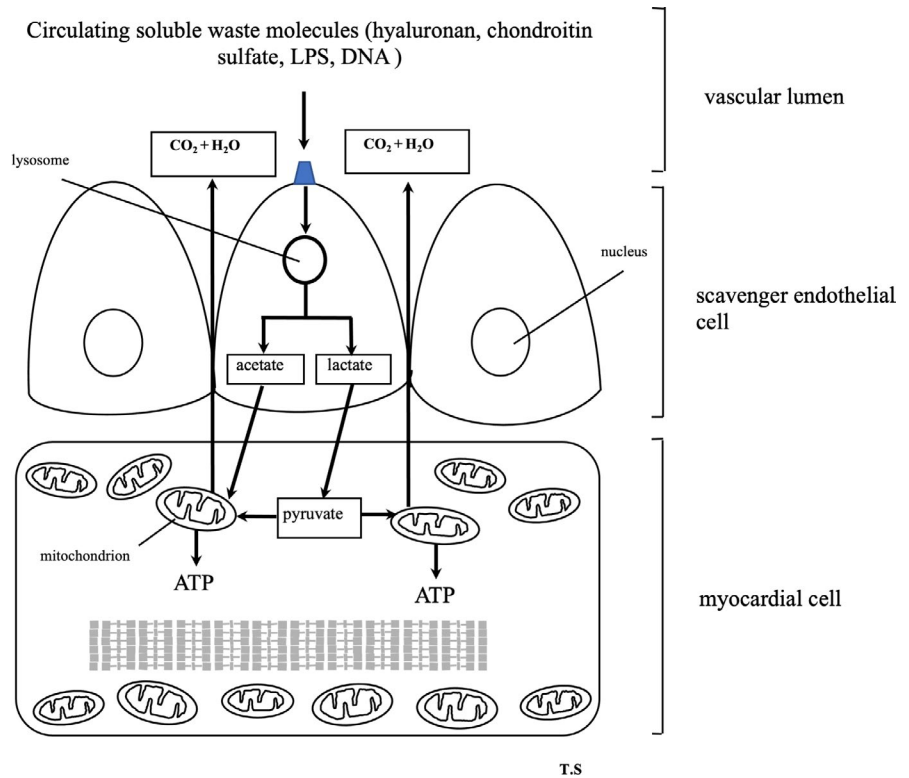
Having morphological traits in common with bone marrow of higher vertebrates, the teleost head kidney is considered to be the major blood-forming (hematopoietic) organ in fish (Hansen & Zapata, 1998; Meseguer et al., 1995; Rombout et al., 2005). The hematopoietic interstitium is interspersed by numerous venous sinusoids that are part of a renal portal system that receives blood from the caudal vein and/or segmental veins of the trunk, depending on fish species (Press & Evensen, 1999; Yancheva et al., 2016; Zapata, 1979). The sinusoidal vessels also surround the renal tubule together with the peritubular capillaries originating from the efferent glomerular arterioles. Ultrastructural examination of kidney from rainbow trout head kidney has revealed that the sinusoids are lined by a flattened endothelium with macrophages resting on the endothelial cells (Dannevig et al., 1994; Ferguson, 1984). The sinusoidal endothelial cells have a well-developed endocytic apparatus, with many coated pits along the luminal plasma membrane, numerous intracellular electron-translucent vesicles and large lysosomal-like dense bodies. These endothelial cells are actively engaged in the blood clearance of circulating macromolecules in several salmonid species as seen in Figure 2 (i.e., rainbow trout and Atlantic

salmon) (Dannevig et al., 1994; Smedsrod et al., 1993). Gelatinized collagen extracted from salmon skin and labelled with  $^{125}\text{I}$ -tyramine cellobiose was eliminated very effectively from blood following intravenous injection in Atlantic salmon. The majority of recovered radioactivity was found in kidney, and examination of kidney sections after injection of fluorescence-labelled collagen showed accumulation of fluorochrome almost exclusively in discrete vesicles in sinusoidal lining cells. No co-localization of simultaneously injected fluorescence-labelled collagen and fluorescence-labelled 3- $\mu\text{m}$  latex beads was observed, suggesting that the denatured collagen was endocytosed by endothelial cells and not by the macrophages (Smedsrod et al., 1993). A series of studies in charr and rainbow trout have demonstrated that soluble scavenger receptor ligands, such as chemically modified proteins, lipoproteins and dsRNA (e.g., FSA, DNP-HSA, acLDL and oxLDL), are rapidly distributed to and retained in the kidney following intravenous injections (Dannevig & Berg, 1978; Dannevig et al., 1990; Froystad et al., 1998, 2002; Gjoen & Berg, 1992a, 1993; Seternes et al., 2002; Smedsrod et al., 1984; Vo et al., 2019). By the use of cell separation techniques, it was found that the major uptake of radiolabelled ligands took place in a population of small non-phagocytic cells with a lower density than kidney macrophages (Dannevig & Berg, 1978; Dannevig et al., 1990). Furthermore, fluorescence microscopy of sections of kidney after injection of fluorescence-labelled acLDL (Gjoen & Berg, 1992b) revealed uptake of fluorescence mainly by flattened sinusoidal lining cells, with no fluorescence observed in larger macrophage-like cells of the tissue. In fact, when radiolabelled DNP-HSA was added to 3-day-old cultures of rainbow trout kidney macrophages, no uptake or binding of ligand was measured (Dannevig et al., 1990). However, uptake of intravenously injected DNP-HSA has been demonstrated in macrophage-like cells of kidney by the use of immunohistochemistry (Dannevig et al., 1994). Phagocytosis of FSA-coated particles has also been reported in rainbow trout macrophages in vitro, and particle uptake could be significantly inhibited by preincubation of



**FIGURE 2** Scavenger endothelial cell in Atlantic salmon kidney (a) 24 hr after intravenous injection of FITC-labelled formaldehyde-treated albumin and in Atlantic cod heart (b) after intravenous injection of FITC-labelled LPS from the fish pathogenic bacteria *Vibrio salmonicida*. Both soluble ligands known to be taken up by receptor-mediated endocytosis in scavenger endothelial cells of vertebrates (Seternes et al., 2002). Photo: Tore Seternes

**FIGURE 3** Cartoon showing tentative coupling of SEC scavenger function and fuelling of cardiomyocytes in cod. Major connective tissue polysaccharides (chondroitin sulphate and hyaluronan), after being released from the tissues to the circulation and foreign soluble molecules as LPS and DNA after injection, are rapidly endocytosed by SEC. The degradation products from hyaluronan and chondroitin sulphate (acetate and lactate) are transferred to cardiomyocytes and utilized as mitochondrial fuel to produce ATP. The final products CO<sub>2</sub> and H<sub>2</sub>O are released to the circulation (modified from Seternes, Oynebraten, et al., 2001). The degradation products from endocytosis and metabolism of LPS and DNA are unknown. Particles with a size above 1 µm are taken up by macrophages located elsewhere



cells with scavenger receptor ligands (Froystad et al., 1998). This indicated that both macrophages and sinusoidal cells from salmonid kidney possess scavenger receptors, but that macrophages seem to be of minor importance in the blood clearance of soluble waste molecules.

In addition to uptake of circulating soluble scavenger receptor ligands, the kidney sinusoidal endothelial cells of the salmonid fish effectively endocytose mannose-terminated glycoproteins, such as invertase and ovalbumin (Dannevig et al., 1990, 1994). The kidney sinusoidal endothelial cells of Atlantic salmon were reported to take part, together with macrophages, in the clearance of intravenously injected lipopolysaccharide (LPS) from the salmonid fish pathogen *Aeromonas salmonicida* (Dalmo et al., 1995; Stensvag, Arnesan, et al., 1999; Stensvag, Bogwald, et al., 1999). Taken together, these studies indicate that the kidney sinusoidal endothelial cells of salmonid fishes are important scavenger cells for endogenous and foreign soluble macromolecules that must be eliminated from the blood circulation. Furthermore, functional evidence exists for the presence of scavenger and mannose receptors in these cells.

The endothelial cells are also able to take up smaller particles like colloidal carbon and colloidal HSA (0.2–1 µm) (Dannevig et al., 1994), whereas larger particulate substances such as immune complexes and bacteria are cleared by macrophages and other phagocytic cells (Espenes et al., 1996; Ferguson, 1984). Accumulation of immunomodulatory laminaran (a β-glucan) was studied in Atlantic salmon (Dalmo et al., 1995). After intravenous administration, FITC-laminaran (FITC: fluorescein isothiocyanate) accumulated in macrophages in kidney and spleen. In addition, endothelial cells in the kidney, spleen, liver and intestine contained FITC-laminaran. The tissue distribution of

plasmid DNA after intravenous and intramuscular administration was studied in the Atlantic salmon using both radio tracing and fluorescence microscopy (Tonheim et al., 2008). The majority of plasmid DNA was taken up mainly by the kidney.

*Endocardial endothelial cells of Atlantic cod*

The endocytic capacity of endocardial endothelial cells of cod (*Gadus morhua* L.) is well studied and a tentative cartoon of the proposed function is shown in Figure 3 (Smedsrod et al., 1995; Sorensen et al., 1997, 1998). They contain numerous organelles associated with active endocytosis (Leknes, 1980, 1987; Saetersdal et al., 1974). Intravenously injected radiolabelled gelatinized cod skin collagen was rapidly eliminated from the blood ( $t_{1/2} = 15$  min) and taken up in heart, with minor uptake in other organs (Smedsrod et al., 1995). FITC-labelled cod collagen was found to be internalized via clathrin-coated vesicles in the endocardial endothelial cells of both atrium and ventricle and transported to lysosome-like organelles in the cells. Effective uptake of circulating hyaluronan, procollagen propeptide (PINP), denatured albumin (FSA) and mannose-terminated glycoproteins (cod lysosomal α-mannosidase and yeast invertase) in cod endocardium has also been observed (Sorensen et al., 1997, 2001). In addition, the soluble ligand laminaran was taken up by the cod endocardium in vivo (Dalmo et al., 1996).

The catabolic fate of circulating hyaluronan and the proteoglycan chondroitin sulphate (CSPG) was studied in the Atlantic cod (Seternes, Oynebraten, et al., 2001). Hyaluronan and CSPG were rapidly eliminated from the blood by the endocardial endothelial cells (EECs) of the heart atrium and ventricle. The atrial EECs express a specific hyaluronan binding site that also recognizes CSPG. FSA

inhibited endocytosis of  $^{125}\text{I}$ -CSPG by 65%, indicating that CSPG is also recognized by the scavenger receptor. This article also suggested that acetate released from cod EECs following catabolism of endocytosed hyaluronan and CSPG represents a high-energy metabolite that may fuel cardiomyocytes (Seternes, Oynebraten, et al., 2001) as seen in the tentative cartoon in Figure 3. It has also been shown that endocardial endothelial cells of Atlantic cod remove *Vibrio salmonicida* LPS from the circulation by scavenger receptor-mediated endocytosis (Seternes, Dalmo, et al., 2001). The anatomical distribution of plasmid DNA was determined using both morphological and radio tracing methods after intravenously and intramuscularly injection. Plasmid DNA was rapidly eliminated from the blood by endocardial endothelial cells of the cod heart atrium and ventricle (Seternes et al., 2007).

#### 1.2.4 | Scavenger endothelial cells of halibut and turbot

The uptake and distribution of *Aeromonas salmonicida* LPS in three marine fish species were investigated.  $^3\text{H}$ - and FITC-LPS accumulated in Atlantic cod, turbot and Atlantic halibut (*Hippoglossus hippoglossus*) mainly in heart, spleen and kidney. In turbot (*Scophthalmus maximus*), the ligands were found mainly in kidney, spleen and liver (Dalmo et al., 1998).

#### 1.2.5 | Scavenger endothelial cells of ornamental fish

The endocardial cells of a number of ornamental fishes have been shown to take up several foreign materials from the circulation. Authors have described this type of endocardial cells to be present in firemouth cichlid (*Cichlasoma meeki*), bronze cory (*Corydoras aeneus*) (Leknes, 1981, 1987) and medaka (*Oryzias latipes*) (Lemanski et al., 1975)—and to a minor extent in goldfish (*Carassius auratus*) and lemon tetra (*Hyphessobrycon pulchripinnis*). The endocardial endothelial cells of swordtail and platy have been reported to actively endocytose horse spleen ferritin (Leknes, 2001) and carbon (Nakamura & Shimozawa, 1994). Two structurally and functionally different endothelial cells in the heart of platyfish (*Xiphophorus maculatus*) have been described (Leknes, 2004, 2016). Endothelial cells of the wall and valves of the ventricular aperture come in contact with only a small amount of the blood volume and have no cleansing ability, while the endothelial cells on the muscle trabeculae come in contact with a large part of the blood volume and are highly efficient as blood cleansing tissue (Leknes, 2004). Large amounts of lipofuscin-like pigments were demonstrated in endocardial cells enveloping the heart muscle of platyfish (*X. maculatus*). The author suggests that occurrence of much lipofuscin-like pigments in cardiac endothelial cells provides evidence for that these cells have performed important scavenger functions (Leknes, 2007b). The structure of the bulbus arteriosus in two species of the teleost family Characidae and three from the Cichlidae was described

(Leknes, 2009). One of the cichlid species (*Thorichthys meeki*) was injected intraperitoneally with horse ferritin. The endothelial cell layer of the heart atrium and ventricle displayed high ability to endocytose from the blood, but the corresponding layer in bulbus arteriosus displayed no such uptake (Leknes, 2009, 2011). The structure and cell types in kidney and spleen of Buenos Aires tetra, *Hyphessobrycon anisitsi*, family Characidae, are described (Leknes, 2012). The macrophages and sinusoidal endothelial cells in kidney and spleen were tightly packed by intraperitoneally injected ferritin. The capability and capacity of endocardial tissue in the heart of Pearl gourami (*Trichogaster leerii*) to take up intraperitoneally injected horse spleen ferritin were investigated (Leknes, 2007a). The endocytic endocardial cells of *T. leerii* were restricted to the atrium only. A scavenger receptor expressed by endothelial cells (SREC-II) is a potential pathogen recognition receptor. In a recent study, SREC-II was found to be highly expressed in spleen, skin, gills, thymus and head kidney of the orange-spotted grouper (*Epinephelus coioides*) (Qiao et al., 2020). Expression of SREC-II after *Vibrio parahaemolyticus* infection was significantly upregulated at 12 hr in spleen, head kidney and thymus (Qiao et al., 2020).

## 2 | CULTURE OF ENDOTHELIAL CELLS

A procedure for establishment of purified cultures of atrial endocardial cells has been developed (Koren et al., 1997). When fluorescence-labelled collagen was added to the isolated endocardial cells, fluorescently stained vesicles were observed in the cells already after 10 min. The staining intensity was decreased by pretreatment of cultures with excess amounts of non-labelled denatured collagen, indicating a specific receptor-mediated uptake of the ligand. Similar in vitro receptor inhibition experiment has been undertaken with other scavenger receptor ligands, which underscores the in vivo observations (Seternes et al., 2007; Vo et al., 2019). Further application of in vitro systems using endothelial cells has been exploited. In the report of Garrick, the isolation and culture of capillary endothelial cells from the rete mirabile (a network of small blood vessels that are formed by the branching of a large vessel and that usually reunite into a single trunk) of the American eel (*Anguilla rostrata*) are described (Garrick, 2000). Also, endothelial cells from the endocardium, bulbus arteriosus and veins were isolated in parallel procedures based on those used with the rete. This work of Majeed et al. (2015) reports development of an endothelial cell line from Snakehead murrel (*Channa striatus*) heart. The established cell line has been used for nodavirus propagation (Majeed et al., 2015). The study of Martin-Armas et al. (2008) describes uptake of LPS and oligonucleotides in cultured Atlantic cod scavenger endothelial cells, and if immunomodulatory molecules like CpG-oligonucleotides, poly I:C and LPS affect the scavenger activity and/or production of immune-modulating molecules of the cells. The study shows that SECs respond differently to the different immunomodulators used and that their important clearance activity as scavenger cells can be regulated by the use of immunomodulators.

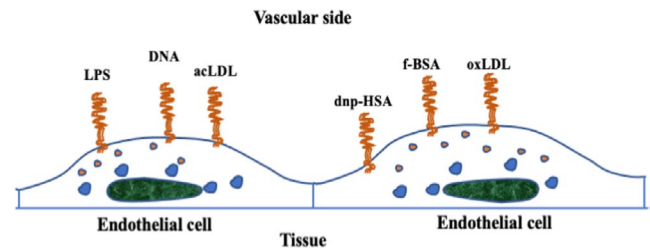


## 2.1 | Molecular markers of SEC in fish

While functional studies have proven the presence and distribution of SEC in different fish species, a major limitation is the lack of identification and characterization of phenotypic markers (receptors, cell membrane molecules) and genotypic signature (gene expression). Until now, studies in higher vertebrate species must be relied on, even though the distinction between certain leucocytes and SEC is not evident (Lalor et al., 2006). It has been proposed that cellular fenestrations (pores up to approx. 200 nm) is the best phenotypic feature of SEC. Liver SEC (in mammals) fenestrations act as a sieving barrier to control the extensive exchange of material between the blood and the liver parenchyma (Satchell & Braet, 2009). The pores can be filled with glycocalyx which contribute to modulated permeability. To study the fenestrations, electron microscopy or advanced nanoscopic examination is needed. Other cell characteristics of certain subtypes of SEC may be their morphology which appear as “high” when studied by light or electron microscopes. This subtype is called high endothelial scavenger cells. This type has also been observed in numerous fish species—especially in the heart (Dalmo et al., 1996). It is speculated that these cells possess a unique ability to promote the recruitment of naïve lymphocytes (Jackson, 2003).

Several studies have been conducted to find markers of mammalian SEC. Since the expression of phenotypic markers differs during SEC development, infection and pathology and is indeed dependent on anatomical residence, it has been challenging to find distinct markers of SEC which are endocytically active—taking up soluble anionic molecules such as acetylated LDL (Lalor et al., 2006). Liver/lymph node-specific ICAM-3-grabbing integrin (L-SIGN), which share homology with DC-SIGN (dendritic cell-specific ICAM-3 grabbing non-integrin), has been proposed to be a good candidate to differentiate hepatic SEC from SEC in other anatomical sites (Cormier et al., 2004). At the moment, the easiest way to characterize SEC in fish is by their selective endocytic activity of SEC ligands, plus electron microscopic analysis—preferably scanning electron microscopy.

The SEC possess scavenger receptors (SR), as seen in Figure 4, which also function as pattern recognition receptors (PRR) recognizing molecules with repeating residues, and the classical chemically modified LDL. It is agreed to use the following terminology to describe SA: “Scavenger receptors are cell surface receptors that typically bind multiple ligands and promote the removal of nonself or altered-self targets. They often function by mechanisms that include endocytosis, phagocytosis, adhesion, and signaling that ultimately lead to the elimination of degraded or harmful substances.” The scavenger receptors are not exclusive to SEC since a variety of different cells express SA. The SA family comprises several classes (SRA-H), where class L, subtype 1, is remarkably conserved during phylogeny (PrabhuDas et al., 2017). This receptor class has been shown to bind, among hundred different ligands, plasma cholesterol, albumin, vitamin D-binding protein and retinol-binding protein. Nonetheless, a phylogenetic study of class A SR, known to recognize modified lipoproteins, has been performed. This study identified five members of the class A SR, which were suggested to



**FIGURE 4** Scavenger endothelial cells are equipped by scavenger receptors which bind an array of molecules such as LPS (bacterial lipopolysaccharides), DNA (deoxyribonucleic acids), acLDL (acetylated low-density lipoproteins), dnp-HSA (dinitrophenylated human serum albumin), f-BSA (formalin-fixed bovine serum albumin) and oxLDL (oxidized low-density lipoproteins). The SEC contains numerous endosomes (orange dots) and lysosomes (blue dots). Cell nuclei are marked in green

have a common ancestor—despite variable amino acid sequences (Whelan et al., 2012). This finding was confirmed in another study (Yap et al., 2015). The remarkable diversity of SA throughout the animal kingdom applies indeed to fish. But since they sense a broad range of different substances, it is difficult to do targeted functional studies on each SR class by, for example, administration of chemically modified substances or other ligands. This means that the present review, describing the anatomical distribution of SEC on basis on their uptake of SEC-specific ligands, does not discriminate between the different SR found in fish. Another issue is that several types of cell of express SR, implying that identification has to be verified by, for example, light microscopy to track the endocytosed ligands in the endothelial linings.

## 3 | CONCLUSION

All vertebrates examined are furnished with a population of special SEC that plays a role in the catabolism of physiologic and non-physiologic soluble waste macromolecules. Judging from the ligands that are endocytosed, SEC in all seven vertebrate classes appear to express the collagen  $\alpha$ -chain receptor and the scavenger receptor. In addition, the hyaluronan- and mannose receptors are observed in SEC of mammalia (several species) and Osteichtyes (salmon and cod). Like LEC in mammals, SEC in all vertebrate classes are geared to endocytosis of soluble macromolecules; phagocytic uptake of particles is taken care of mainly by macrophages. The most primitive vertebrates (hagfish, lamprey and ray) carry their SEC in gill vessels; phylogenetically younger fishes (salmon, carp, cod and plaice) carry their SEC in either kidney or heart; and all terrestrial vertebrate SEC are found exclusively in the liver.

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**DATA AVAILABILITY STATEMENT**

This review does not contain primary experimental results; thus, there is no need to convey data management involving open access availability of results. Upon acceptance, this manuscript as preprint will be deposited at UiT library's data storage facility.

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