Oxylipins: Role in Stem Cell Biology

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Abstract: Oxylipins, oxygenated fatty acid derivatives, are well-established stress mediators acting in auto- and paracrine manner. Eicosanoids, the most studied branch of oxylipins, are produced from twenty carbon polyunsaturated fatty acids (PUFAs). In vertebrates, they are synthesized mainly by lipoxygenase (LOX), cyclooxygenase (COX) and cytochrome P450-type monooxygenases. In corals, besides COX and LOX enzymes, the oxidation of arachidonic acid (AA) is catalyzed by natural fusion proteins, comprised of a LOX domain and a catalase related peroxidase domain, allene oxide synthase (AOS) or hydroperoxide lyase (HPL). Although oxylipins are well studied in vertebrate stem cells, their role in stem cells originating from marine invertebrates remains unexplored. Here, we present an overview of major oxylipin pathways in vertebrates and marine invertebrates, and discuss their potential role in invertebrate stem cells.

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1. Introduction

There is a growing interest in invertebrate stem cells (SCs) due to their high toti- and pluripotency which makes them suitable model systems to investigate fundamental biological processes, such as cell fate, senescence, regeneration and cell reprogramming (Ballarin et al. 2018). Due to the simplicity of marine invertebrates, it is easier to track the expression of genes, test different compounds on differentiation/regeneration and discover underlying mechanisms of SCs (Manni et al. 2019). For instance, colonial ascidians are ideal organisms for the study of tissue regeneration and development because of their diverse reproductive strategies, relatively short lifespan, simple morphological and genomic organization, and easy experimental use. In addition, the high diversity of invertebrates creates an opportunity to use them as a source of novel natural products, including bioactive lipid mediators, which can be used to treat cancer, infections, autoimmune and inflammatory-related diseases, and can potentially be implemented in regenerative medicine (Palanisamy et al. 2017).

A group of bioactive oxylipins derived from arachidonic acid (AA), eicosanoids, are identified as important auto- and paracrine mediators of tissue repair and regeneration that act by regulating the stem cell biochemistry in vertebrates. Only a limited number of oxylipin studies have been conducted on invertebrates used for SC research (Kassmer et al. 2020). Screening and targeting of oxylipins from invertebrates would provide novel insights into the molecular mechanisms necessary

for either stemness or differentiation of SCs in marine invertebrates. For instance, profiling of oxylipins and tracking their secretion to surrounding tissues would reveal spatio-temporal distribution of oxylipins and their regulatory role in self-renewal and/or differentiation of SCs. This knowledge can be beneficial in the future studies of SCs across different species.

This review summarizes the status of oxylipin studies in invertebrate SC model systems and focuses on corals as the most studied model of oxylipin biosynthesis in invertebrates.

2. Oxylipin Pathways in Animals

Eicosanoids are the main group of oxylipins in animals synthesized from AA (C20: 4ω6) and other C20 polyunsaturated fatty acids (PUFAs) by fatty acid dioxygenases, e.g., lipoxygenase (LOX) and cyclooxygenase (COX), or monooxygenases, such as cytochrome P450 epoxygenases, respectively (Figure 1) (Brash 1999; Rouzer and Marnett 2003; Nelson et al. 2013).

In mammals, eicosanoids and other bioactive lipids are highly potent short-lived molecules that initiate signaling cascades and gene expression by binding to their corresponding receptors or being ligands for transcription factors. Activation of gene expression regulates cellular events, including cell proliferation and differentiation, and different physiological and pathological processes, e.g., inflammatory-related diseases and cancer. In addition to AA, other PUFAs, such as eicosapentaenoic acid (EPA, C20: 5ω3) and docosahexaenoic acid (DHA, C22: 6ω3), are the precursors for important bioactive lipids, e.g., resolvins and protectins (Serhan et al. 2002, 2008), which mediate the resolution of inflammation in animals.

The complexity of eicosanoid pathways is necessary to modulate cellular processes in a cell type and a metabolic state manner. On the other hand, the high variability of eicosanoids and sophisticated regulatory networks makes eicosanoid research challenging.

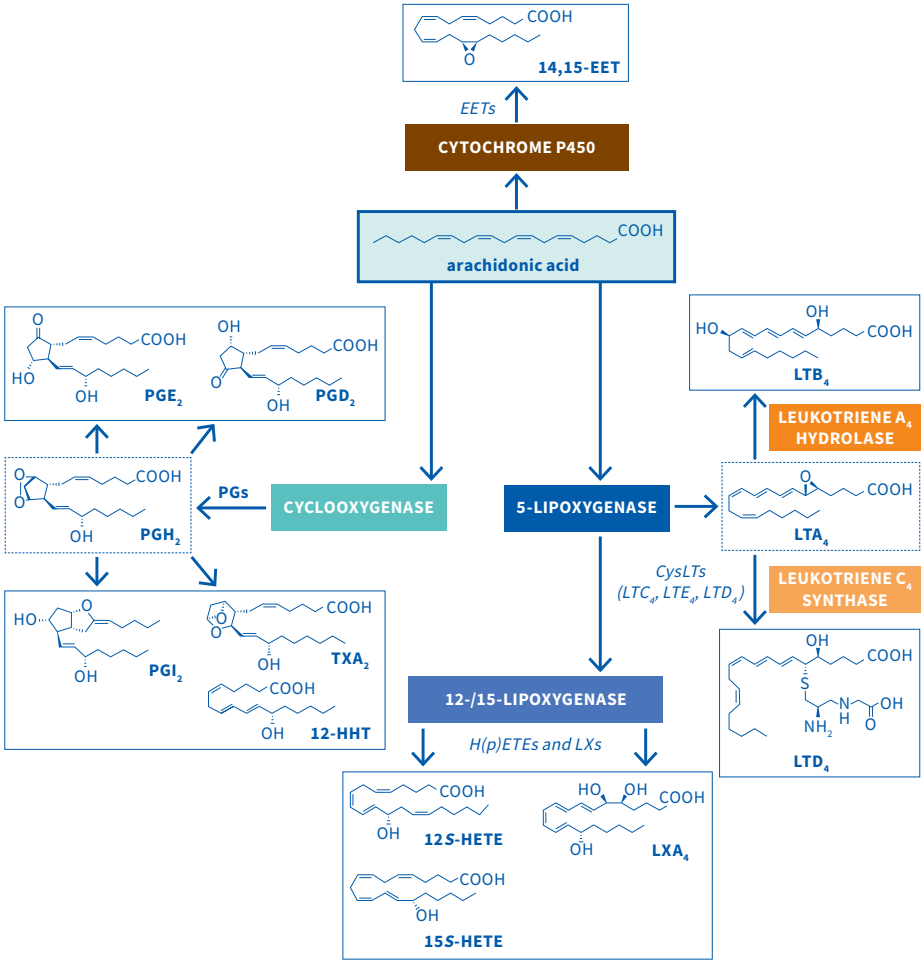

Figure 1. Biosynthetic routes of eicosanoids in animals. Arachidonic acid (AA) is released from cellular membranes by phospholipases in response to a variety of stimuli and converted to eicosanoids by cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP450) monooxygenase pathways. The COX pathway gives rise to prostaglandins (PGs), the LOX pathway produces hydroxy-eicosatetraenoic acids (HETEs), lipoxins (LXs) and leukotrienes (LTs), and CYP450 synthesizes epoxy-eicosatetraenoic acids (EETs). CysLT—cysteinyl leukotrienes; EET—epoxy-eicosatetraenoic acid; HETE—hydroxy-eicosatetraenoic acid; HHT—hydroxy-heptadecatrienoic acid; LT—leukotriene; LX—lipoxin; PG—prostaglandin; TX—thromboxane. Source: Graphic by authors.

2.1. Lipoxygenase

LOXs (E.C. 1.13.11.-) are non-heme iron containing dioxygenases that catalyze the regio- and stereo-specific peroxidation of PUFAs containing at least one *cis*,*cis*-1,4-pentadiene system to form biologically active mediators (Brash 1999). LOXs are classified in terms of their positional specificity. Animal LOXs are arachidonate 5-, 8-, 11-, 12- and 15-LOXs that catalyze the conversion of AA into corresponding 5-, 8-, 11-, 12- and 15-hydroperoxy-eicosatetraenoic acids (HpETEs) (Brash 1999). Depending on the species and cell type-specific expression of enzymes, the content and distribution of eicosanoids vary. Thus far, the LOX with 11*R*-specificity has been identified only in marine invertebrates, such as hydra (Di Marzo et al. 1993), sea urchins (Hawkins and Brash 1987) and corals (Di Marzo et al. 1996; Varvas et al. 1999; Mortimer et al. 2006). In terrestrial organisms, the prevalent stereo-configuration of LOX products is *S*, while *R* stereospecificity is more pronounced in marine invertebrates.

HpETEs or their reduced derivatives, hydroxy-eicosatetraenoic acids (HETEs), are potent pro- or anti-tumorigenic agents and mediate cell migration due to their chemotactic properties and also. For example, 5- and 12-HETEs synthesized by 5- and 12-LOX, and 13-hydroxy-octadecadienoic acid formed by 15-LOX, respectively, are involved in the proliferation and inhibition of apoptosis, angiogenesis, cancer invasion and metastasis, while 15- and 8-HETE formed by 15-LOX-2 and 8-LOX are involved in the differentiation, growth arrest and induction of apoptosis (Pidgeon et al. 2007; Moreno 2009). In addition, lipid mediators generated in 5-LOX pathway mediate atherosclerosis and allergic inflammation (Haeggström 2018). Most importantly, HpETEs are precursors of many downstream biosynthetic routes, such as the leukotriene and lipoxin pathways (Figure 1), which are involved in the initiation and resolution of inflammation, respectively (Funk 2001; Serhan et al. 2002; Haeggström and Funk 2011).

2.2. Cyclooxygenase

Cyclooxygenases (COXs), also known as prostaglandin endoperoxide synthases (E.C. 1.14.99.1), are another oxygenation route converting AA to prostaglandins (PGs). All vertebrates have two COX isozymes, a constitutively expressed COX-1 and an inducible COX-2 (Funk 2001). Both COXs catalyze the formation of PGG_2 via cyclooxygenase activity and its reduction to PGH_2 via peroxidase activity (Rouzer and Marnett 2003; Schneider et al. 2007). The main differences between COX-1 and COX-2 are their genetic regulation and function (Rouzer and Marnett 2005; Blobaum and Marnett 2007). The formation of PGH_2 by COXs is a rate-limiting step in its downstream conversion to prostaglandin E_2 (PGE_2), $PGF_{2\alpha}$, and PGD_2, as well as the conversion to prostacyclin (PGI_2) and thromboxane A_2 (TXA_2) by corresponding isomerases or synthases (Figure 1) (Rouzer and Marnett 2009). Prostanoids are

involved in inflammatory processes, wound healing, tissue regeneration and cardiovascular processes. Therefore, the inhibition of COX results in reduced inflammation, pain and fever (Flower 2006). Non-steroidal anti-inflammatory drugs (NSAIDs) have anti-inflammatory and pro-resolving effects through the inhibition of COX-2 (Vane and Botting 1998). In conferring their biological function, e.g., evoking an inflammatory response after injury, PGs have opposite effects. For example, depending on the timing and course of inflammation, they can either induce vasoconstriction ($PGF_{2\alpha}$, TXA_2, TXB_2) or vasodilation (PGE_1, PGE_2, PGI_2), inhibition of platelet aggregation (PGD_2, TXA_1, PGE_1, PGI_2) (Murakami 2011; Ricciotti and FitzGerald 2011) or aggregation of platelets (PGE_2) (Howie et al. 1973; Kobzar et al. 1997). Elevated levels of PGE_2 sensitize spinal neurons, which results in an increased sense of pain (Grace et al. 2014), causing fever via the hypothalamus-mediated manner (Coceani and Akarsu 1998), and are involved in the complex process of labor (Kelly et al. 2009).

3. Coral Eicosanoids

Corals are invertebrate animals (Kingdom *Animalia*; phylum *Cnidaria*; class *Anthozoa*) (Hyman 1940) that are divided into two major subclasses: reef-building *Hexacorallia* and soft corals *Octocorallia* (Zhang 2011), both comprised of azooxanthellate or zooxanthellate, the latter living in symbiosis with unicellular algae, *Symbiodinium sp.* species.

Coral oxylipin research started with the detection of large quantities of PGs and PG-esters (2–3% of dry weight) in the soft coral *Plexaura homomalla* (Weinheimer and Spraggins 1969). Thereafter, a plethora of eicosanoids have been discovered, which vary depending on the species and location (Corey et al. 1973, 1987, 1988; Varvas et al. 1993, 1999; Brash et al. 1987). In soft corals, AA is an abundant fatty acid (10–25%), being the primary precursor of eicosanoids (Imbs et al. 2006; Imbs and Yakovleva 2011). To a lesser degree (3–10%), AA also contributes to the fatty acid content of stony corals (Latyshev et al. 1991; Dunn et al. 2012; Figueiredo et al. 2012; Funk 2001). Released AA is metabolized by COX (Varvas et al. 1994; Koljak et al. 2001; Valmsen et al. 2001) or LOX (Mortimer et al. 2006; Brash et al. 1996) into PGs or H(p)ETEs, respectively (Figure 2). In addition to 11*R*-LOX (Eek et al. 2012; Mortimer et al. 2006; Järving et al. 2012), corals contain catalase-related allene oxide synthase-8*R*-lipoxygenase (AOS-LOX) and hydroperoxide lyase-8*R*-lipoxygenase (HPL-LOX) fusion protein pathways (Koljak et al. 1997).

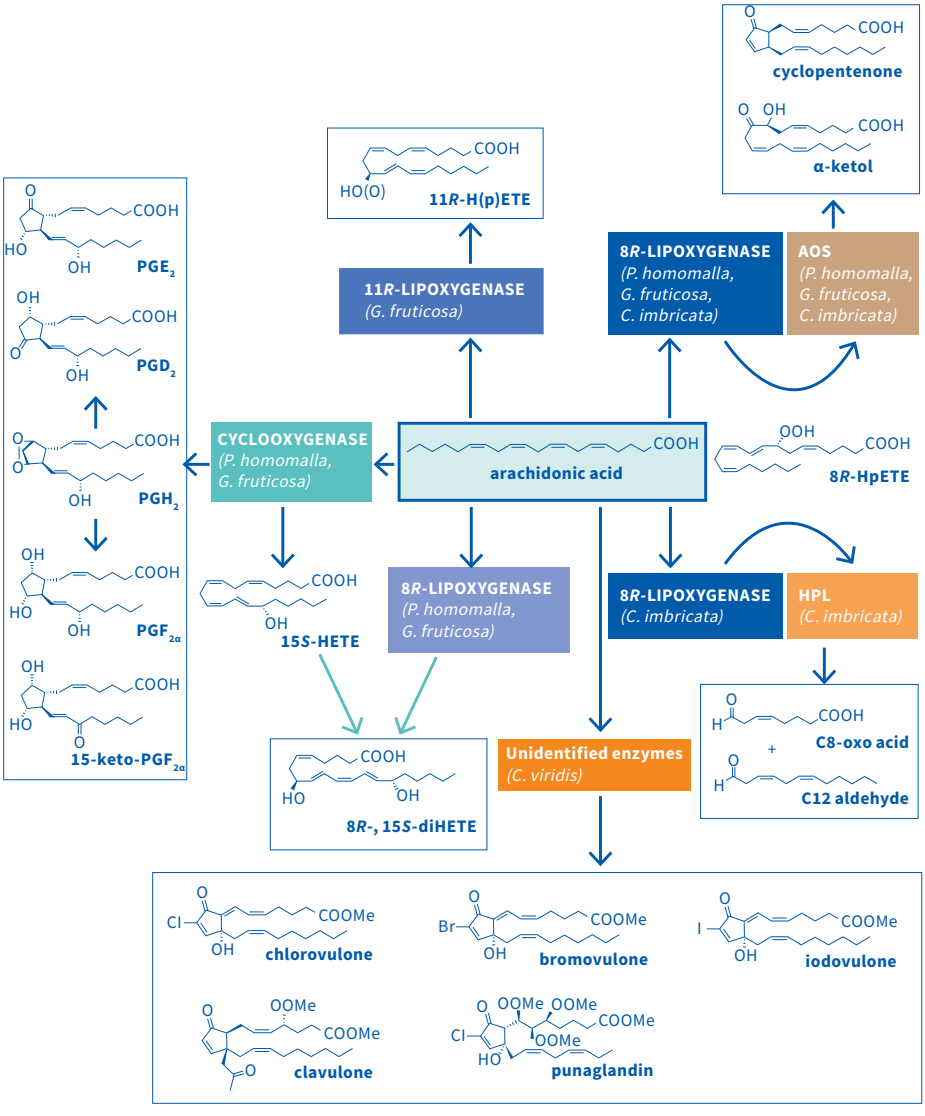

Figure 2. The eicosanoid pathways identified in soft corals (Varvas et al. 1993, 1999). AOS, allene oxide synthase; H(p)ETE—hydro(pero)xyeiocosatetraenoic acid; HPL—hydroperoxide lyase; PG—prostaglandin. *C. imbricata—Capnella imbricata; C. viridis—Clavularia viridis; G. fruticosa—Gersemia fruticosa; P. homomalla—Plexaura homomalla.* Source: Graphic by authors.

In principle, the coral AOS-LOX and HPL-LOX pathways are similar to the plant LOX pathways, except the fact that separately expressed and structurally distinct plant LOX, P450-type AOS and HPL metabolize only C18 PUFAs, e.g., linoleic acid

(Wasternack 2007). Initially, the cyclopentenone synthesized by coral AOS was thought to be the precursor of coral PGs, but the cloning and characterization of functional coral COXs indicated the existence of parallel oxygenation routes (Koljak et al. 2001; Valmsen et al. 2001). Even though *P. homomalla* contains a considerable amount of PGs, incubations with the tissue homogenate and exogenous AA do not produce PGs (Corey et al. 1973, 1988). In contrast, homogenates of *G. fruticosa* give rise to optically active PGs in vitro (Varvas et al. 1993, 1999). In addition, the soft coral *Clavularia viridis* converts AA to different cyclopentenone-type compounds, such as clavulones (preclavulone A) (Corey et al. 1987), bromovulones and iodovulones (Figure 2) (Honda et al. 1987; Watanabe et al. 2001). Although AOS-LOXs are not involved in the biosynthesis of coral PGs, they still might contribute to the production of clavulone-like derivatives. For today, the AOS-LOX pathway is identified in soft corals *P. homomalla*, *G. fruticosa,* and *C. imbricata,* while 11*R*-LOX is expressed only in *G. fruticosa*. In addition, no COX activity and PGs have been detected from *C. imbricata*. Although the sequence data implies the presence of AOS-LOX in soft and stony corals (Lõhelaid and Samel 2018), the fusion protein with the lyase activity is identified only in *C. imbricata*. Altogether, this data is indicative of species-specific eicosanoid biosynthesis.

The current literature on coral eicosanoids contains data on the identification of naturally occurring compounds (Corey et al. 1973, 1985; Varvas et al. 1993, 1994), the elucidation of metabolic pathways involved in their biosynthesis (Brash et al. 1987; Corey et al. 1987; Koljak et al. 1997, 2001; Varvas et al. 1999), and the effects of lipid extracts or isolated compounds on other systems (Hashimoto et al. 2003). For today, only the role of PGs in the defense of the coral *P. homomalla* against predators has been proposed (Pawlik et al. 1987; Gerhart 1991; O'Neal and Pawlik 2002; Whalen et al. 2010). In regard to the LOX activity in other marine invertebrates, it was demonstrated that 8*R*-HETE induces the maturation of starfish oocytes (Meijer et al. 1986) and 11*R*-HpETE is involved in the regeneration and bud formation of *Hydra vulgaris* (Di Marzo et al. 1993). In spite of the wide occurrence of different oxylipins (hydroxy fatty acids, PGs and their derivatives, etc.) in invertebrates (Rowley et al. 2005; Brash et al. 1987), their exact functions in those organisms remain unclear.

Coral Fusion Proteins in the Arachidonic Acid Pathway

In the arachidonate metabolism of corals, fusion proteins comprised of N-terminal catalase-like allene oxide synthase (AOS) or hydroperoxide lyase (HPL) and C-terminal 8*R*-LOX domains catalyze the conversion of AA via 8*R*-HpETE to allene oxide (Koljak et al. 1997; Lõhelaid et al. 2008, 2014a) or short-chain aldehydes (Teder et al. 2015), respectively (Figure 2). The 3D structure of the AOS-LOX fusion protein (Gilbert et al. 2008), as well as separately expressed AOS and LOX domains (Oldham et al. 2005a, 2005b; Neau et al. 2009), have been determined. Even though the structure of HPL-LOX has not been resolved, the differences in the substrate

specificity and catalytic properties between HPL and AOS (Teder et al. 2017, 2019) indicate distinct regulation and roles of corresponding fusion proteins in vivo.

Several transcriptomic studies of stony corals have reported the increased expression of the *AOS-LOX* gene in response to white band disease (Libro et al. 2013), elevated UV radiation (Aranda et al. 2011) and temperature (Polato et al. 2013). However, transcriptomes lack information about expressed proteins and their activity. A targeted study with the soft coral *C. imbricata* demonstrated the elevated levels of AOS-LOX metabolites and increased gene expression in response to wounding (Lõhelaid et al. 2014a) and temperature (Lõhelaid et al. 2014b). In parallel, the levels of HPL-LOX mRNA and metabolites remained stable or even decreased. To date, involvement of the AOS-LOX pathway in the stress response of corals is evident, however, the biological importance of HPL-LOX remains elusive. Short-chain aldehydes also known as "green leaf volatiles" play an essential part in the communication and stress signaling of plants. In addition, aldehydes have antibacterial and antifungal properties due to their molecular attributes. Therefore, HPL-LOX-derived aldehydes may serve a housekeeping role, including defense against biotic stressors.

4. Eicosanoids in Stem Cells

SCs are undifferentiated progenitor cells with the ability to differentiate into specialized cell types and regenerate. Eicosanoids are best known for their inflammatory and immune-modulating properties, however, their ability to affect the cell fate has increased their importance in SC biology. Eicosanoids act in an auto- and paracrine manner to promote proliferation, migration, and differentiation of SCs which contribute to the tissue repair, regeneration and other cellular processes. For example, eicosanoids mediate the differentiation of SCs at each step of wound healing (Berry et al. 2017). Due to the diversity of bioactive lipids and other regulators, the role of eicosanoids in determining the fate of SCs is not very well understood.

The roles of PUFAs and eicosanoids have been studied in mammalian mesenchymal stem cells (MSCs) (Jang et al. 2012; Yun et al. 2009b, 2011; Ern et al. 2019; Kim et al. 2009b; Rinkevich et al. 2009), hematopoietic stem cells (HSCs) (Hoggatt and Pelus 2010), embryonic stem cells (ESCs) (Liou et al. 2007; Yanes et al. 2010; Yun et al. 2009b; Rajasingh and Bright 2006; Kim et al. 2009a), neural stem cells (NSCs) (Katura et al. 2010; Wada et al. 2006; Wiszniewska et al. 2011; Katakura et al. 2009, 2013; Beltz et al. 2007; He et al. 2009; Sakayori et al. 2011; Kawakita et al. 2006; Jung et al. 2006; Goncalves et al. 2010; Sasaki et al. 2003), endothelial progenitor stem cells (EPC) (Kawabe et al. 2010; Herrler et al. 2009) and others (Table 1). For instance, MSCs constitutively express COX, PGE_2 synthase (PGES) (Jang et al. 2012; Kleiveland et al. 2008), 5-LOX, and 12-LOX (Fang et al. 2015), giving rise to PGs, LTs and LXs, respectively. In addition, MSCs express different PG receptors, EP1-EP3, FP, and IP (Rinkevich et al. 2009). MSCs and eicosanoids are studied due to their involvement in immune-modulating and

inflammatory-related processes (Bernardo and Fibbe 2013). In addition to MSCs, human periodontal ligament stem cells (hPDLSCs) produce PGE_2, PGD_2 and $PGF_{2\alpha}$ as well as specialized pro-resolving mediators (SPMs), e.g., different resolvins, protectin D1, maresins, and LXB_4 (Berry et al. 2017).

Table 1. Bioactions of eicosanoids in stem cells.

Fatty Acid or Eicosanoid	Stem Cell Type	Effects	References
Linoleic acid	Embryonic stem cells	Enhanced proliferation	(Kim et al. 2009a)
Arachidonic acid	Neuronal stem cells	Enhanced proliferation	(Vaca et al. 2008; He et al. 2009; Sakayori et al. 2011; Kawakita et al. 2006; Sakamoto et al. 2007)
Eicosapentaenoic acid	Neuronal stem cells	Improved differentiation	(Katakura et al. 2009)
Docosahexaenoic acid	Neuronal stem cells	Improved differentiation, increased proliferation	(Beltz et al. 2007; Katakura et al. 2009, 2013; Kan et al. 2007)
Prostaglandin E_1, E_2	Hematopoietic stem cells	Inhibited proliferation	(Gidali and Feher 1977; Kurland et al. 1978; Motomura and Dexter 1980)
	Embryonic stem cells	Enhanced proliferation, inhibited apoptosis	(Yun et al. 2009b; Liou et al. 2007; Hou et al. 2013)
	Human umbilical cord blood-derived mesenchymal stem cells	Enhanced proliferation	(Yun et al. 2011; Jang et al. 2012)
	Neuronal stem cells	Enhanced proliferation	(Jung et al. 2006; Goncalves et al. 2010; Sasaki et al. 2003)
	Bone marrow-derived cells	Improved endothelial differentiation	(Zhu et al. 2011)
	Tendon stem cells	Improved osteogenic differentiation	(Liu et al. 2013)
Δ12,14-prostaglandin J_2	Embryonic stem cells	Inhibited proliferation	(Rajasingh and Bright 2006)
15d-prostaglandin J_2	Neuronal stem cells	Regulation of proliferation	(Katura et al. 2010)
Leukotriene B_4	Neuronal stem cells	Regulation of proliferation, promoted differentiation to neurons	(Wada et al. 2006; Wiszniewska et al. 2011)
	Hematopoietic stem cells	Enhanced proliferation, inhibited apoptosis	(Chung et al. 2005)
Leukotriene D_4	Embryonic stem cells	Enhanced proliferation	(Kim et al. 2010)
Lipoxin A_4	Neuronal stem cells	Inhibited proliferation	(Wada et al. 2006)
	Human periodontal ligament stem cells	Enhanced proliferation, migration and wound healing	(Berry et al. 2017)
	Human dental apical papilla	Immunomodulation, proliferation, wound healing. Attenuated chemokine and growth factor secretion	(Gaudin et al. 2018)
	Bone marrow-derived mesenchymal stem cells	Resolution of inflammation and injury, bacterial clearance, increased SC growth.	(Fang et al. 2015; Tsoyi et al. 2016)
Lipoxin B_4	Bone marrow-derived mesenchymal stem cells	Radioprotection	(Walden 1988)
Neuroprotectin D_1	Embryonic stem cells	Improved neuronal and cardiac differentiation	(Yanes et al. 2010)
Thromboxane A_2	Adipose tissue-derived mesenchymal stem cells	Enhanced proliferation, promote differentiation to smooth-muscle-like cells	(Yun et al. 2009a; Kim et al. 2009b)

Table adapted from (Kang et al. 2014) and modified accordingly.

The role of eicosanoids has been extensively studied in tissue repair and generation. Overall, LTs and PGD_2 have a negative regulatory effect on tissue repair, while other lipid mediators, such as other PGs and LXs, promote healing (Esser-von Bieren 2019). It should be noted that the same type of lipid mediators may be differently regulated during proliferation, differentiation and migration of SCs (Rinkevich et al. 2009).

Modulation of eicosanoid pathways has an impact on the fate of SCs. For instance, the inhibition of COX and LOX pathways manifests in the pluripotency of ESC (Yanes et al. 2010). In contrast, supplementation of fatty acids and their derivatives promote proliferation and differentiation of mouse ESC (Yanes et al. 2010; Kim et al. 2009a). It is also known that SPMs lose their therapeutic effect when 5-LOX, 12-LOX and 15-LOX activities are attenuated (Romano et al. 2019).

4.1. Roles of Eicosanoids in Vertebrate Stem Cell Biology

4.1.1. The LOX Pathway in Stem Cells

The expression of 5-LOX and biosynthesis of LTs are increased in differentiated ESCs. Inhibition of the 5-LOX pathway results in impaired vasculogenesis by ESCs (Finkensieper et al. 2010). A downstream lipid mediator of the 5-LO pathway, LTB_4, induces the differentiation and anti-apoptotic effects of CD34+ HSCs and the inhibition of LTA_4H and its receptor, BLT2, resulted in self-renewal of HSCs (Chung et al. 2005). In addition, 12/15-LOX and its products, 12-HpETE and 15-HpETE, play important role in skin wound healing (Hong et al. 2014).

4.1.2. The COX Pathway in Stem Cells

The impact of PGs on the proliferation of HSCs was reported back in the 1970s (Feher and Gidali 1974; Gidali and Feher 1977). It was shown that PGE_2 released by monocytes or macrophages suppresses the proliferation of myeloid SCs in vitro. In addition, the presence of PGE_2 and higher expression of its receptors are linked to stimulation of angiogenesis and early state of inflammation (Ern et al. 2019). MSCs secrete different bioactive molecules, including PGE_2, that guide the polarization of pro-inflammatory to anti-inflammatory macrophages, resulting in lowered levels of inflammation (Prockop 2013). PGE_1 promotes the differentiation of HSCs to mature granulocytes and attenuates the production of macrophages. Similarly to PGE_2, PGI_2 is necessary to angiogenesis and the inhibition of PGI_2 synthase results in impaired wound healing (He et al. 2008). A short-term stimulation with PGE_2 enhances the proliferation of MSCs, while longer treatments inhibit growth. In contrast, PGD_2 has a growth-inhibitory effect in spite of the duration of the incubation (Ern et al. 2019). The development of human smooth muscle-like cells from adipose tissue-derived MSCs is controlled by another prostaglandin, TXA_2 (Yun et al. 2009a). Overall, inhibition of COX pathways by NSAIDS, e.g., aspirin (Liu et al. 2014) and ibuprofen (Goren et al. 2017), results in lower levels of TXs and PGs which delay the wound healing and self-renewal.

4.1.3. Pro-Resolving Mediators in Stem Cells

SPMs are formed in the cross-play between COXs, LOXs and other pathways or in the presence of drugs. For instance, LXA_4 can be formed cooperatively via 5-LOX and 12-/15-LOX pathways (Figure 1). It is evident that different SCs contain the biosynthetic machinery to produce different SPMs which can be potentially involved in the immune-modulating and anti-inflammatory properties of SCs (Romano et al. 2019). For example, MSCs secrete LXA_4 which regulates anti-inflammatory and pro-resolving processes (Rinkevich et al. 2009; Tsoyi et al. 2016). In fact, exogenous or MSC-derived LXA_4 contribute to the recovery from acute lung injury (Fang et al. 2015). Moreover, LXA_4 significantly enhances the wound healing capacity of hPDLSCs (Berry et al. 2017) and regulates the proliferation and differentiation of NSCs (Wada et al. 2006). Protectin D1 (also known as neuroprotection D1) promotes cardiac and neuronal differentiation and is essential in the regeneration of nerve cells (Yanes et al. 2010).

4.2. Model Systems for Marine Invertebrates

There are four main invertebrate adult SC models—the "big four": *Porifera*, *Cnidaria*, *Platyhelminthes* (flatworm), and *Tunicata* (Rinkevich et al. 2021). The PUFAs and eicosanoid pathways present in *Cnidaria* were discussed in detail above (see 3. Coral Eicosanoids). Although more than 250 fatty acids are determined in *Porifera*, there are no higher PUFAs, thus no traditional eicosanoids are present (Rod'kina 2005; Monroig et al. 2013) (Figure 3). In comparison, the main substrate PUFAs in *Platyhelminthes* (Angerer et al. 2019; Makhutova et al. 2009) and *Tunicates* are EPA and DHA, however, only trace amounts of AA are found (Mimura et al. 1986). It should be noted, that as in *Cnidarians*, there might be high variance in PUFA content between different species. In parallel, also the presence of LOXs varies between invertebrate species. For instance, no LOX sequences have been found in *Porifera* (Horn et al. 2015).

Dugasia tigrina was used as a planarian (*Platyhelminthes*) model to study regeneration by DHA and DHA-derived oxylipins from vertebrates (Serhan et al. 2012) (Figure 3). The ability to enhance the tissue regeneration by a lipid mediator, macrophage mediator in resolving inflammation (MaR1), indicates conserved regulatory roles and pathways of DHA-derived mediators. Inhibition of 12-LOX resulted in attenuated regeneration and formation of MaR1, suggesting that the 12-LOX pathway may play important role in *D. tigrina* (Figure 3). In addition, the genome of *Schistosoma japonicum* revealed conserved sequences of LOX, LTA_4H and putative receptors for LTB_4, cysteinyl-LTs, PGE_2 and PGF_2, indicating that these pathways may play a role in the physiology of planarian (Zhou et al. 2009). However, *Schmidtea mediterranea* does not contain any similar sequences to COX or LOX known in animals based on the PlanMine sequence database (Rozanski et al. 2019) (personal data).

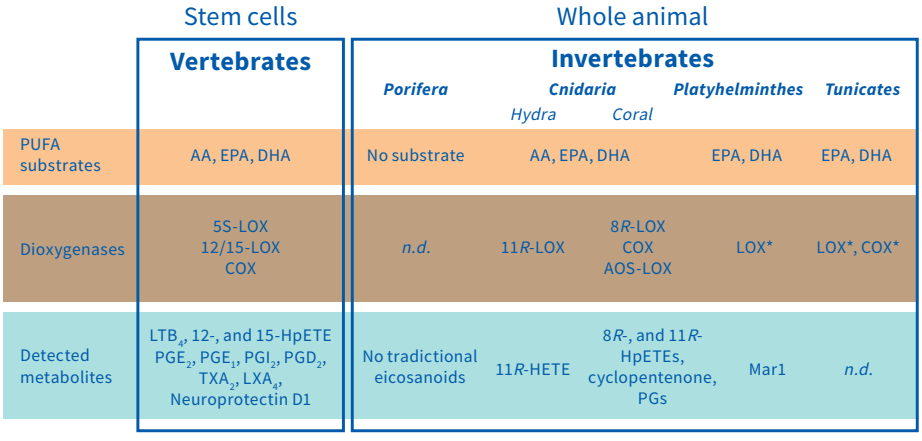

Figure 3. The PUFA-dependent oxylipin pathways in vertebrate stem cells and in model organisms of invertebrates. * Predicted based on the gene sequence; *n.d.*—not determined. Source: Graphic by authors.

The PUFA composition of tunicates reveals that the most abundant PUFA substrates are EPA and DHA (Carballeira et al. 1995; Hou et al. 2021). Even though coral COX-like sequences exist in tunicates (Järving et al. 2004), it remains unknown if they encode functional dioxygenases and what is their catalytic specificity. Recently, it was shown that the germ cell migration and chemotaxis in *Botryllus schlosseri* is 12*S*-HETE-dependent (Kassmer et al. 2020). Unfortunately, only 12*S*-HETE was in the focus of their study and other HETEs remained untested. Furthermore, a *B. schlosseri* LOX sequence was described with a sequence identity of around 50% positives to human 5-LOX, 12-LOX and 15-LOX (Kassmer et al. 2020). The genome of closely related *Botrylloides diegensis* supports the presence of a single LOX gene in both species (Voskoboynik et al. 2013; Blanchoud et al. 2018). The sequence of *B. schlosseri* LOX contains conserved iron-coordinating amino acids and the amino acid determinant of regiospecificity (either *S* or *R*) suggests the presence of LOX with the *S*-specificity. However, only the end of the C-terminal domain without the N-terminal PLAT and part of the catalytic domains was present in the sequence (personal data). Thus, the presence of catalytically functional LOX in *B. schlosseri* needs to be confirmed by future studies.

Although major advances have been made in sequencing invertebrate genomes and transcriptomes, the prediction of bioactive metabolites only based on sequence data is not accurate due to highly conserved domains between dioxygenases with different catalytical specificities and biological roles, such as LOXs (Lõhelaid and Samel 2018). Additional experiments with dioxygenases need to be performed to supplement the sequence data. In conclusion, despite the progress in the field,

very little is known about oxylipin biosynthesis or metabolites in invertebrate model systems.

Common precursor PUFAs for the oxylipin synthesis in vertebrate and invertebrate systems demonstrate the evolutionary requirement of lipid mediators in the physiology of animals (Figure 3). As in vertebrates the effect of different eicosanoids on the fate of SCs are clearly demonstrated (Table 1), it is likely that these processes in marine invertebrates are driven by ancestor genes and similar mediators.

4.3. Potential Role of Eicosanoids in the Stem Cells of Marine Invertebrates

In contrast to vertebrates, SCs in marine invertebrates are disseminated throughout the organism and instead of uni- or oligopotency, they possess pluri- and totipotent capabilities. Another unique property of invertebrate SCs is their ability to trans-differentiate from one cell type to other (Rinkevich et al. 2009). It occurs when a significant amount of SCs is needed, specifically during budding, regeneration and in response to severe abiotic or biotic stress (Rinkevich et al. 2009).

In all species studied to date, lipid mediators mediate important adaptation responses to cellular stress. Organisms continuously sense and respond to environmental conditions to maintain their homeostasis under changing conditions and survive. Biological stress can be defined as an adverse condition or force which disturbs the homeostasis and normal functioning of an organism (Jones et al. 2010). Overall, external stressors may be biotic, such as pathogens, or physical, such as temperature, salinity, water, nutrient deprivation, chemicals and pollutants, oxidative stress, mechanical stress and radiation.

The initial wound response in animals aims for rapid and efficient isolation of the wound to minimize both the loss of vital fluids and environmental challenges (Proksch et al. 2008; Rodriguez et al. 2008; Ariel and Timor 2013; Palmer et al. 2011; Maffei et al. 2007). In multicellular organisms, regeneration involves the repair of tissues/organs after injury and homeostatic renewal. The spatio-temporal immune cell activation is essential in regenerative response and its adequate regulation defines the regenerative success. The initial step in response to the incision in marine invertebrates, including corals, aims for rapid and efficient provisional plugging of the wound, similar to vertebrates (Palmer et al. 2011). On a cellular level, the wound repair in vertebrates has four phases: (1) hemostasis/coagulation, (2) inflammation, (3) proliferation and (4) remodeling (Singer and Clark 1999; Schultz et al. 2011; Maderna and Godson 2009). The same wound repair phases are observed in *Cnidarians* (Reitzel et al. 2008; Olano and Bigger 2000; Palmer et al. 2008). Coral wound response includes the recruitment of granular amoebocytes (Mydlarz et al. 2008; Palmer et al. 2008), which are important in pathogen clearance. Acting cooperatively, eicosanoids mediate the initial stages of wound response and the onset and end of the inflammatory phase of wound repair, promoting cell migration

and modulating the central signal pathways involved in cell cycle control (Moreno 2009). Oxylipins are also involved in coral wound response (Lõhelaid et al. 2014a), but their effect on marine invertebrate stem cells is not known. Furthermore, innate immune response and regeneration are inter-connected processes during tissue repair (Aurora and Olson 2014). As pointed out before, 11*R*-HETE enhanced the tentacle regeneration and bud formation of decapitated *Hydra vulgaris* (Di Marzo et al. 1993) indicating its direct cellular regulator effect. The distribution of stem cells and molecular regulation of stemness in *Hydra* is complex (Hobmayer et al. 2012). Unfortunately, it is not known which cells are responding to this biomolecule and what is the underlying molecular mechanism.

In addition, the levels and production of eicosanoids in vertebrates are low and tightly controlled (Dennis and Norris 2015; Serhan and Chiang 2008), whereas corals contain an enormous amount of various oxylipins (Weinheimer and Spraggins 1969). Thus, the high production of oxylipins, such as PGE_2 in *P. homomalla*, could contribute to the differentiation of SCs and also increase the regenerative capacity of invertebrates.

4.4. Challenges in the Stem Cell Biology of Marine Invertebrates

Currently, we lack basic knowledge about oxylipins and oxylipin-mediated processes in marine invertebrates and their distribution in different cell populations, including stem cells. The main practical limitations for efficient studies are the absence of (1) SC definition in invertebrates, (2) adequate biomarkers to distinct cell populations, (3) developed protocols for SC isolation, and (4) proper knowledge of how to culture SCs and create SC lines. In addition, there are well-established protocols for extraction and analysis of different lipid subclasses (Hou et al. 2021), however, specific know-how, equipment and a certain amount of SCs for the proper detection are still required. Apart from the identification and profiling of oxylipins, it is challenging to determine the role of each of the individual oxylipins on the stem cells due to the high number of oxylipin derivatives and complexity of intracellular oxylipin pathways. Nevertheless, constantly improving state-of-the-art technology and methodology as well as greater networking opportunities contribute to the advancement of SC research.

5. Conclusions

Oxylipins, including eicosanoids, are short-lived lipid mediators, they act locally in an auto- and paracrine manner to control proliferation, migration, and differentiation of vertebrate SCs which contribute to tissue repair, regeneration and other cellular processes. Based on current knowledge, we propose that oxylipins are also involved in the renewal, proliferation and differentiation of marine invertebrate SCs. Still, due to a variety of lipid mediators and other regulators, and lack of

studies, the role of eicosanoids in determining the fate of marine invertebrate SCs is far from being clear. For example, it is difficult to translate the function if there is a high variation in oxylipin content between different species and the regio- and stereoisomers of lipid mediators might have different or even opposite effects. Studies on marine invertebrate genomes and transcriptomes are able to give some clues, but they are insufficient to predict the specificity nor functionality of dioxygenases. To date, sequence data from different organisms are emerging, however, we lack systematic studies in different marine invertebrate species. For instance, profiling of oxylipin pathways and biological actions of PUFAs and oxylipins on model organisms and their SCs should be performed. Thus, only basic research on invertebrate SCs is able to define the compounds produced in model systems and the role of applied eicosanoids.

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