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REVIEW ARTICLE

Adhesion molecules in gamete transport, fertilization, early embryonic development, and implantation—role in establishing a pregnancy in cattle: A review

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Abstract

Cell–cell adhesion molecules have critically important roles in the early events of reproduction including gamete transport, sperm–oocyte interaction, embryonic development, and implantation. Major adhesion molecules involved in reproduction include cadherins, integrins, and disintegrin and metalloprotease domain-containing (ADAM) proteins. ADAMs on the surface of sperm adhere to integrins on the oocyte in the initial stages of sperm–oocyte interaction and fusion. Cadherins act in early embryos to organize the inner cell mass and trophectoderm. The trophoblast and uterine endometrial epithelium variously express cadherins, integrins, trophinin, and selectin, which achieve apposition and attachment between the elongating conceptus and uterine epithelium before implantation. An overview of the major cell–cell adhesion molecules is presented and this is followed by examples of how adhesion molecules help shape early reproductive events. The argument is made that a deeper understanding of adhesion molecules and reproduction will inform new strategies that improve embryo survival and increase the efficiency of natural mating and assisted breeding in cattle.

KEYWORDS
ADAM, adhesion molecules, cadherin, early reproductive events, integrin, review

1 | INTRODUCTION

Cell–cell adhesion molecules have important roles in the organization of tissues and organs during development and in the maintenance of cellular and tissue integrity throughout life (Gallin, 1998; Taneyhill, 2008). Changes to normal cell–cell adhesion often lead to alterations in cellular and tissue functions. This can include uncontrolled cellular growth and metastasis (Adorno-Cruz & Liu, 2019). Indeed, much of what is known about adhesion molecules and cellular function has come from studies in cancer biology (Buchanan et al., 2017; Edwards, Handsley, & Pennington, 2008; Najy, Day, & Day, 2008; Shiomi, Lemaitre, D'Armiento, & Okada, 2010; Sousa, Pereira, & Paredes, 2019; Zadka, Kulus, & Piatek, 2018).

Adhesion molecules are critically involved in the early events of reproduction (Evans, 1999; Klentzeris, 1997; H. Wang & Dey, 2006). This includes gamete transport, fertilization, embryonic development, and implantation. The main families of adhesion molecules associated with reproduction are integrins, cadherins, and disintegrin and metalloprotease domain-containing (ADAM) proteins (Evans, 1999). Some adhesion molecules appear to act at specific stages of early reproduction (e.g., ADAMs), while others are involved from gamete transport through to implantation (e.g., integrins). Certain adhesion molecules seem to have a particularly important function in early reproduction in one species. An example is trophinin, which appears to have a clear role in implantation in humans, although it has been reported in other species (Fukuda & Sugihara, 2008).

In cattle, the failure of a conceptus to attach to the uterine epithelium (implantation) and establish a pregnancy is the major source of reproductive loss (D'Occhio, Campanile, & Baruselli, 2019; Sponchiado et al., 2019). Both the trophoblast epithelium and uterine endometrial epithelium express adhesion molecules (Kokkinos, Murthi, Wafai, Thompson, & Newgreen, 2010). These behave in a manner similar to "velcro" and achieve initial apposition between the trophoblast and uterus. It is hypothesized that improper expression of adhesion molecules by the trophoblast, uterus, or both is the underlying cause for a high proportion of early pregnancy failures in cattle.

This review first provides a general background on different families of adhesion molecules. The review then considers the role of specific adhesion molecules in gamete transport, fertilization, embryonic development, and implantation. The argument is made that a deeper understanding of the role of adhesion molecules in early reproductive events will inform new strategies to increase the efficiency of both natural mating and assisted breeding. There is particular mention of adhesion molecules in cattle for two primary reasons. First, the failure of embryos to survive, implant, and establish a pregnancy is the major cause of reproductive failure in cattle. Second, cattle have major economic and social importance in global food systems (D'Occhio et al., 2019). Hence, increasing pregnancy outcome in cattle with natural mating and/or by the use of assisted reproductive technology has both biological and social significance.

The field of adhesion molecules is vast and a goal of this review is to equip readers with a good working knowledge of the main adhesion molecules that are linked with early reproductive events. We hope this will encourage research that could lead to the next step change in the proportion of embryos that produce a pregnancy. A second goal is to illustrate how cellular processes in reproduction can share the same basic mechanisms as analogous cellular processes associated with diverse physiological functions. It is important that reproductive biologists are aware that fundamental cellular and molecular mechanisms can be common across different biological pathways. The review includes many seminal articles that are highly cited. It is trusted that this comprehensive resource provides a valuable point of reference on adhesion molecules and their role in early reproductive events.

2 | FAMILIES OF ADHESION MOLECULES

2.1 | Disintegrin and metalloprotease domain-containing proteins

The family of ADAM proteins has over 35 members which function as cell adhesion molecules and/or proteases (Black & White, 1998; Rocks et al., 2008; Seals & Courtneidge, 2003; J. M. White, 2003). ADAMs are involved in cell–cell and cell–extracellular interactions associated with angiogenesis, platelet aggregation, cell migration, muscle development, tumor growth, immunity, and other cellular processes (Bax et al., 2004; Dreymueller, Theodorou, Donners, & Ludwig, 2017; Edwards et al., 2008; Lambrecht, Vanderkerken, & Hammad, 2018; Rocks et al., 2008; Seals & Courtneidge, 2003; Zadka et al., 2018). ADAMs are transmembrane glycoproteins and occur as functional heterodimers (α and β subunits) in many tissues and across different species (Bronson, Fusi, Calzi, Doldi, & Ferrari, 1999; Edwards et al., 2008). They have a multidomain structure that is highly conserved (Edwards et al., 2008; Seals & Courtneidge, 2003; Figure 1).

One of the ADAM domains has homology with disintegrins (Figure 1). The latter are proteins identified in snake venom that

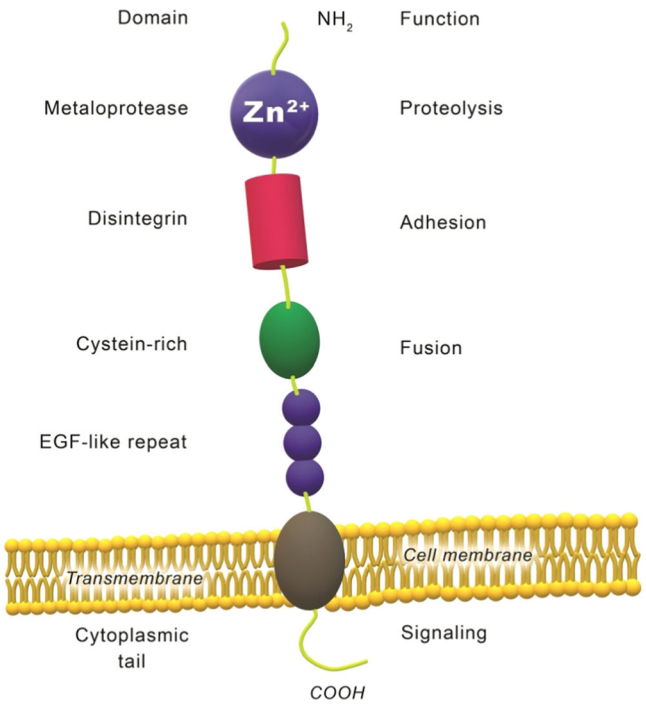

FIGURE 1 Diagrammatic representation of the disintegrin and metalloprotease domain-containing (ADAM) proteins family of cell–cell adhesion molecules. The ADAMs family of transmembrane proteins belong to the zinc protease superfamily; specifically, the metzincin subgroup and further subgroup the adamalysins. The multidomain structure of ADAMs includes a prodomain (adjacent to NH_2 terminus), metalloprotease domain, disintegrin domain, cysteine-rich domain, EGF-like domain, transmembrane domain, and a cytoplasmic tail. The metalloprotease domain (adamalysins) is involved in extracellular matrix degradation and remodeling, while the disintegrin domain is involved in integrin receptor binding which facilitates cell–cell adhesion. The metalloprotease domain and disintegrin domain give ADAMs their name (a disintegrin and metalloprotease). The cysteine-rich domain was shown in *Xenopus laevis* to regulate ADAM protease function (Smith et al., 2002) and it may also participate in adhesion. EGF-like domains are a common feature of adhesion molecules and proposed roles include ligand recognition and adhesion (Kansas et al., 1994). The specific role(s) of the EGF-like domain in ADAMs has yet to be clearly elucidated. The transmembrane domain anchors ADAMs to the cell. The conserved cytoplasmic tail has binding sites for intracellular signal transduction proteins and is involved in intracellular signaling (Stone, Kroeger, & Sang, 1999). EGF, epidermal growth factor

interact with integrins, a second family of adhesion molecules discussed below. The disintegrin domain of ADAMs, therefore, has adhesion properties and is involved in cell–cell and cell–extracellular matrix interactions (Eto et al., 2002; Tomczuk et al., 2003; Zhu, Bansal, & Evans, 2000). Disintegrins in snake venom have a RGD (Arg-Gly-Asp) integrin-binding sequence (Blobel, 1997). Human ADAM15 has a RGD motif and, in other mammals, the binding of ADAMs to integrins can involve different amino acid motifs (Eto et al., 2002; Takahashi, Bigler, Ito, & White, 2001; Wong, Zhu, Prater, Oh, & Evans, 2001; Yuan, Primakoff, & Myles, 1997). In mice, these include QDE (Gln-Asp-Glu; Zhu et al., 2000) and DECD (Asp-Glu-Cys-Asp; Chen & Sampson, 1999). An analogous functional motif in the guinea pig is TDE (Thr-Asp-Glu; Myles, Kimmel, Blobel, White, & Primakoff, 1994). Extracellular matrix proteins bound by ADAMs include collagen, fibronectin, gelatin, and laminin (Martin, Eynstone, Davies, Williams & Steadman, 2002; Seals & Courtneidge, 2003; J. M. White, 2003).

ADAMs that have been associated with reproduction include ADAM1 (fertilin α; initially named PH-30), ADAM2 (fertilin β), and ADAM3 (cyritestin; Blobel et al., 1992; Edwards et al., 2008; Evans, 1999; Frayne & Hall, 1999; Myles et al., 1994; Myles, Primakoff, & Bellve, 1981). Functional fertilin is a heterodimer comprised of fertilin α and fertilin β (Evans, 1999, 2001; Wong et al., 2001). It is found on the surface of sperm and the disintegrin domain, which is located on fertilin β, enables sperm to interact with integrins on the oolemma of oocytes (Bronson et al., 1999). ADAMs on the surface of sperm appear to also be involved in sperm transport and this is discussed below.

2.2 | Integrins

Integrins are transmembrane heterodimers comprised of α- and β-subunits (Bachmann et al., 2019; Humphries, Byron, & Humphries, 2006; Humphries, Travis, Clark, & Mould, 2004; Hynes, 1992; Figure 2). A total of 18 α-subunits and 8 β-subunits have been identified which form 24 α–β integrin combinations (Barezyk et al., 2010; Campbell & Humphries, 2011; Shimaoka, Takagi, & Springer, 2002). Two main functions of integrins are involvement in cell–cell adhesion and the attachment of cells to extracellular matrix proteins including laminin, collagen, vitronectin, and fibronectin (Barczyk, Carracedo, & Gullberg, 2010; Seguin, Desgrosellier, Weis, & Cheresh, 2015; Shimaoka et al., 2002). The short cytoplasmic tail of integrins is linked to the actin cytoskeleton through talin (Bouaouina, Harburger, & Calderwood, 2011; Iwamoto & Calderwood, 2015; Figure 2).

This allows signaling between the cytoskeleton and the extracellular matrix (Bouaouina et al., 2011; Das, Ithychanda, Qin, & Plow, 2014; Hynes, 1992; Iwamoto & Calderwood, 2015). Changes in the interaction of integrins with the extracellular matrix can lead to abnormal cell migration and tissue invasion in some cancers (Desgrosellier & Cheresh, 2010; Hamidi & Ivaska, 2018; Seguin et al., 2015). This has made integrins a potential target for anticancer therapies (Desgrosellier & Cheresh, 2010; Seguin et al., 2015). The integrin-associated cell-surface protein tetraspanin CD9 is important for the action of integrins (Reyes, Cardenes, Machado-Pineda, & Cabanas, 2018; Termini & Gillette, 2017; Zhu & Evans, 2002; Ziyyat et al., 2006; Figure 2).

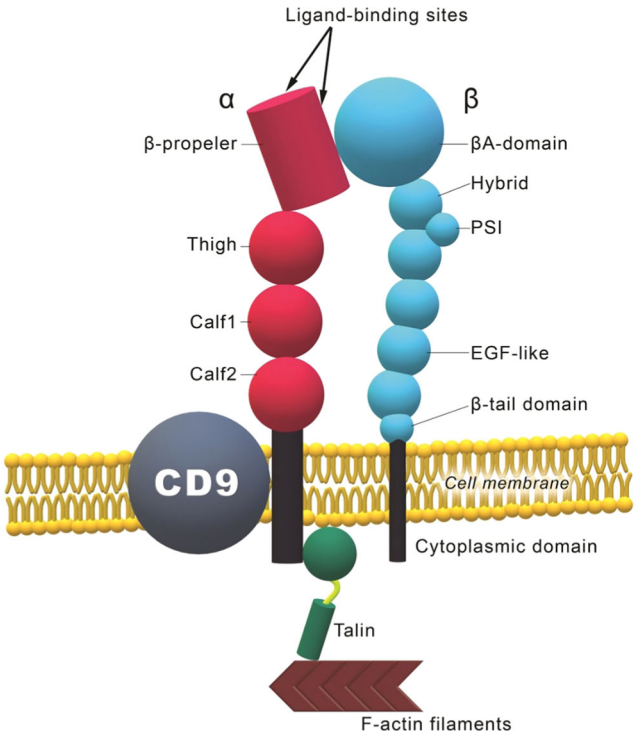

FIGURE 2 Diagrammatic representation of the integrin family of cell–cell adhesion molecules. Integrins are heterodimers that comprise noncovalently associated α-subunit (red) and β-subunit (blue; Campbell & Humphries, 2011; Pan, Zhao, Yuan, & Qin, 2016; Takada, Ye, & Simon, 2007). They have an extracellular domain, a transmembrane domain, and cytoplasmic domain. The α-subunit domains include a β-propeller, a thigh, and two calf domains. Some integrins have an I-domain inserted in the β-propeller. The α-subunit also has homologous repeating units which have Ca^{2+} and Mg^{2+} binding sites important for ligand binding (Yamnuik & Vogel, 2005; Zhang & Chen, 2012). The α-subunit transmembrane domain is relatively short and is involved in integrin affinity through α- and β-subunit interactions. The α-subunit cytoplasmic domain is also relatively short and interacts with talin, which in turn links to F-actin filaments of the cytoskeleton. This facilitates signaling between the cytoskeleton and extracellular matrix. The extracellular components of the β-subunit comprise a βA-domain (inserted into the hybrid domain) that is homologous to the α-subunit I-domain and is crucial for ligand binding, a hybrid domain (potentially involved in affinity regulation), a cysteine-rich PSI (plexin, semaphoring, integrin) domain (involved in activation and ligand binding), four epidermal growth factor (EGF) repeats (potentially involved in propagating conformational signals from the membrane/cytosol to the ligand-binding headpiece), a β-tail domain adjacent to the cell membrane (involved in activation; Anthis & Campbell, 2011), and a cytoplasmic domain that interacts with talin that links to F-actin filaments of the cytoskeleton, which influences integrin activation (Calderwood et al., 1999). The function of integrins is fundamentally dependent on integrin-associated cell-surface protein tetraspanin CD9 (Reyes et al., 2018). PSI, plexin, semaphoring, integrin

In reproduction, the expression of integrins in mammals has been demonstrated for sperm (Barraud-Lange et al., 2007), unfertilized oocytes (Fenichel & Durand-Clement, 1998; Takahashi et al., 2000), the trophoblast (Bowen, Bazer, & Burghardt, 1996), and uterus (Bowen et al., 1996; Lessey, 1998; Sueoka et al., 1997; Yoshimura, 1997). Integrins are, therefore, involved from fertilization through to implantation (Bowen & Hunt, 2000; Fleming, Sheth, & Fesenko, 2001; Reddy & Mangale, 2003; Sueoka et al., 1997).

2.3 | Cadherins

Cadherins are a superfamily of more than 100 Ca^{2+}-dependent cell–cell adhesion molecules (Angst, Marcozzi, & Magee, 2001; Gul, Hulpiau, Saeys, & van Roy, 2017; Kemler, Ozawa, & Ringwald, 1989; Koch, Bozic, Pertz, & Engel, 1999; Nollet, Kools, & van Roy, 2000; Yagi & Takeichi, 2000). These transmembrane glycoproteins (Figure 3) have many important roles in cell–cell contact and cell signaling during tissue morphogenesis and also in the maintenance of tissue homeostasis (Gallin, 1998; Gumbiner, 1996; Leckband & Sivasankar, 2012; Maitre & Heisenberg, 2013; Mohamet, Hawkins, & Ward, 2011; Niessen, Leckband, & Yap, 2011; Takeichi, 1995, 1988; Tiwari et al. 2018). Three classical cadherin groups that are named for their tissue distribution and function include epithelial cadherin (E-cadherin), neural cadherin (N-cadherin), and placental cadherin (P-cadherin; Moore, Radice, Dominis, & Kemler, 1999). N-cadherin, for example, has an important role in organizing cell adhesion and movement during the formation of the neural crest in embryogenesis (Derycke & Bracke, 2004; Taneyhill, 2008).

The extracellular region of cadherins consists of five domains that are involved in Ca^{2+}-dependent homophilic (identical molecules apposed on neighboring cells) and heterophilic (other molecules such as integrins on neighboring cells) interactions during cell adhesion and cell sorting (Halbleib & Nelson, 2006; Oda & Takeichi, 2011; van Roy & Bers, 2008; Figure 3).

The intracellular tail, which is most highly conserved, binds with catenins (α- and β-catenins) which, in turn, interact with the actin cytoskeleton (Gooding, Yap, & Ikura, 2004; Gul et al., 2017; Kemler et al., 1989; Ranscht, 1994; Takeichi, 2014; Yap, Brieher, & Gumbiner, 1997; Figure 3). This creates molecular links whereby the intracellular region of cadherins can influence the activity of the extracellular region (Nagafuchi & Takeichi, 1988; Kintner, 1992). Intracellular α-catenin is essential for cadherin function as cells that express cadherin but lack α-catenin do not show cell–cell adhesion and cell signaling properties (Termini & Gillette, 2017). Similar to other families of adhesion molecules (ADAMs, integrins), altered function of cadherins can be associated with tumor growth and metastasis (Sousa et al., 2019). With regard to early reproductive events, cadherins have been assigned roles during fertilization, embryogenesis, and implantation (Bloor, Metcalfe, Rutherford, Brison, & Kimbler, 2002; Derycke & Bracke, 2004; Ranscht, 1994; Vazquez-Levin, Marín-Briggiler, Caballero, & Veiga, 2015).

3 | ADHESION MOLECULES AND REPRODUCTION

The majority of studies on adhesion molecules and reproduction have been carried out in laboratory animals (mouse, rat) and humans. It can be concluded from these studies that adhesion molecules have fundamental roles in early reproductive events that lead to attachment of the trophoblast to the uterus, the initiation of implantation, and the establishment of a pregnancy. As noted above, many of the articles cited below are from studies in laboratory animals and humans and, as a precautionary note, information on the roles of specific adhesion molecules may not necessarily apply across all species. For example, early embryonic development and placentation vary within and between monogastric and ruminant animals. The trophinins would appear to be particularly important adhesion molecules in trophoblast–uterine endometrial epithelium attachment in humans.

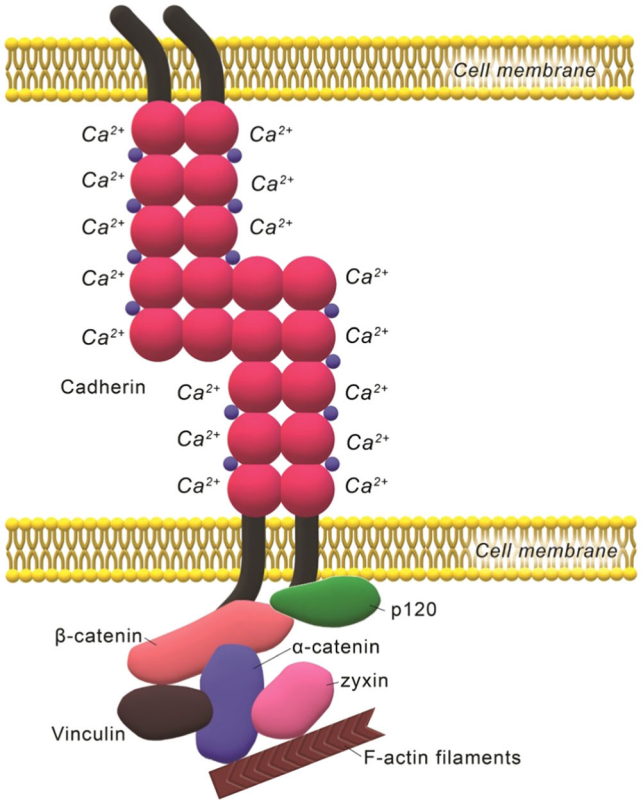

FIGURE 3 Diagrammatic representation of the E-cadherin family of cell–cell adhesion molecules. The extracellular domains of E-cadherin are involved in cell–cell adhesion and in "classical" cadherins comprise five domains often classified as EC1–EC5 from the N-terminus (Leckband & Prakasam, 2006). Cadherins are only stable in the presence of Ca^{2+} which rigidifies the five domains and is also involved in homotrophic adhesion between cadherins on neighboring cells (Boggon et al., 2002; Nagar, Overduin, Ikura, & Rini, 1996). The intracellular domain of E-cadherins interacts with catenins which act as intermediaries and link to F-actin filaments of the cytoskeleton (Gul et al., 2017; Stepniak, Radice, & Vasioukhin, 2009). The link through to the cytoskeleton is important for cell–cell adhesion (Nagafuchi, Ishihara, & Tsukita, 1994; Nagafuchi & Takeichi, 1988)

3.1 | Gamete transport

The role of adhesion molecules in gamete transport is not as extensively researched as the roles in fertilization, embryonic development, and implantation. For sperm, their movement through the epididymides and migration to the oviducts after mating involves interaction with the extracellular matrix. This interaction is thought to be facilitated by adhesion molecules found on the surface of sperm (Blobel, 2000; Cho, 2012; Xiong, Wang, & Shen, 2019). Mouse sperm lacking ADAM3 (Yamaguchi et al., 2009) and E- and N-cadherin (Vazquez-Levin et al., 2015) showed impaired mobility and did not migrate to the oviducts. The adhesion molecule trophinin was shown to be associated with sperm motility in humans (Hatakeyama et al., 2008) and mice (Park et al., 2012). Once sperm arrive at the oviducts, adhesion molecules facilitate the attachment of sperm to the oviductal epithelium (Aviles, Gutierrez-Adan, & Coy, 2010; Frolikova et al., 2016, 2019; Talevi & Gualtieri, 2010). This is an important step that prevents premature capacitation in sperm. Cumulus-oocyte complexes (COCs) also express adhesion molecules (e.g., E-cadherin and N-cadherin) that are thought to be involved with the transfer of COCs to the infundibulum and transport in the oviducts (Caballero et al., 2014; Talbot, Shur, & Myles, 2003; Vazquez-Levin et al., 2015).

3.2 | Fertilization

After sperm penetrate through the zona pellucida (Florman & Wassarman, 1985), they adhere to the oocyte before fusion and penetration. A series of studies undertaken primarily during the 1990s led to the predominant concept that ADAMs (fertilin) present on sperm attach to integrins on the oolema of oocytes (Cho et al., 1998; D'Cruz, 1996; Evans & Florman, 2002; Fenichel & Durand-Clement, 1998; Snell & White, 1996; Figure 4).

The oocyte integrin most often reported to be associated with sperm–oocyte attachment is $\alpha_6\beta_1$ (Almeida et al., 1995; M. S. Chen et al., 1999; Takahashi et al., 2000; Yoshimura, 1997). Sperms were also reported to express $\alpha_6\beta_1$ integrin (Barraud-Lange et al., 2007) and $\alpha_v\beta_3$ integrin (Boissonnas et al., 2010) that participated in sperm–oocyte attachment. It could be concluded from these studies that both male and female gametes express integrins that are involved in the initial interaction between sperm and oocyte. However, the central role of $\alpha_6\beta_1$ in sperm–oocyte attachment was questioned by reports of normal fertilization in knockout mice with oocytes that either lacked all β_1 integrins (He et al., 2003) or α_6 integrin (Miller, Georges-Labouesse, Primakoff, & Myles, 2000). It was also reported that monoclonal antibodies to β_3 integrin and α_v integrin did not prevent the attachment of sperm to β_1 integrin null mice oocytes (He et al., 2003). The experimental approaches in the latter studies have been debated and the balance of evidence remains in support of a role for integrins, and, in particular, $\alpha_6\beta_1$ in sperm–oocyte attachment (Evans, 2009; Okabe, 2018). The above discrepancies amongst reports on integrins could indicate that there is a degree of redundancy in cell adhesion mechanisms that promote initial sperm–oocyte attachment. For example, the extracellular matrix protein vitronectin is present on spermatozoa after capacitation and was proposed to serve as a ligand for sperm attachment to the oocyte, potentially through the integrin $\alpha_v\beta_6$ (Fusi, Lorenzetti, Vignali, & Bronson, 1992).

The action of integrins includes interaction with the integrin-associated cell-surface protein tetraspanin CD9 (Reyes et al., 2018; Termini & Gillette, 2017; Zhu & Evans, 2002; Ziyyat et al., 2006; Figure 2). A role for CD9 in the attachment of sperm ADAM2 to oocyte $\alpha_6\beta_1$ was demonstrated in mice using CD9 knockout models (Kaji et al., 2000; Miyado et al., 2000; Le Naour, Rubinstein, Jasmin, Prenant, & Boucheix, 2000) and with the use of monoclonal antibodies to CD9 (M. S. Chen et al., 1999; Stein, Primakoff, & Myles, 2004). The involvement of CD9 in sperm–oocyte attachment

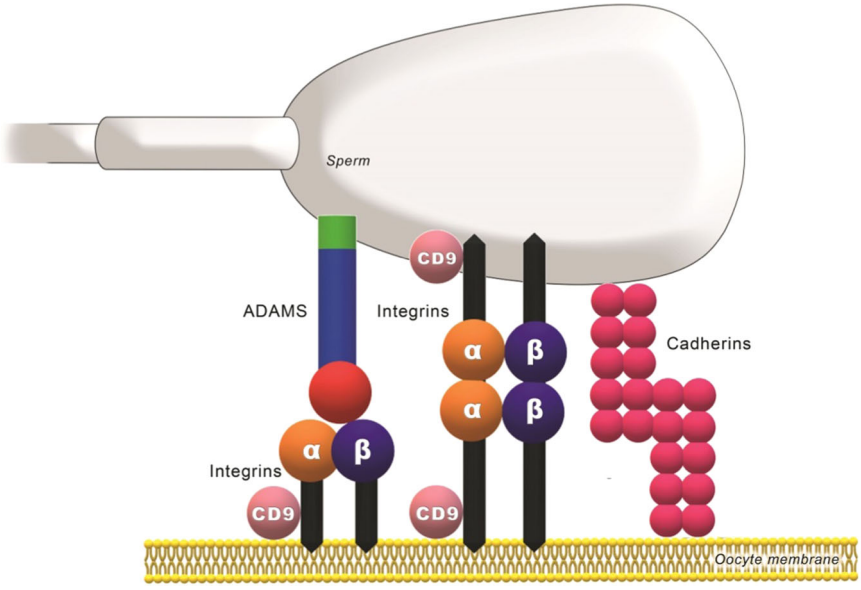

FIGURE 4 Diagrammatic representation of cell–cell adhesion molecules shown to be involved in initial attachment between sperm and oocyte oolema. The families of adhesion molecules involved include ADAMs, cadherins, and integrins. Different families are considered to be involved in sperm–oolema attachment in different species. ADAM, a disintegrin and metalloproteinases

was subsequently demonstrated for other mammals (Kaji & Kudo, 2004; Rubinstein, Ziyyat, Wolf, Le Naour, & Boucheix, 2006; Stein et al., 2004). It was proposed that the role of CD9 is to induce a redistribution of adhesion molecules including $\alpha_6\beta_1$ on the surface of oocytes, as a process that precedes sperm–oocyte fusion (Jegou et al., 2011; Ziyyat et al., 2006). Combining the above information, it would appear that while ADAMs on sperm and $\alpha_6\beta_1$ on oocytes are players in sperm–oocyte adhesion, CD9 is fundamentally required for gamete attachment, fusion, and fertilization (Bianchi et al., 2014; Jegou et al., 2011). Molecules involved in the actual sperm–oocyte infusion process include JUNO and IZUMO (Aydin, Sultana, Li, Thavalingam, & Lee, 2016; Bianchi, Doe, Goulding, & Wright, 2014; Evans, 2002; Georgadaki, Khoury, Spandidos, & Zoumpourlis, 2016; Sutovsky, 2009; Vjugina & Evans, 2008).

3.3 | Embryonic development

Early embryos undergo a process called compaction, which leads to the formation of two distinct morphological features—the inner cell mass (ICM) and trophectoderm (Collins & Fleming, 1995; Pauken & Capco, 1999; Saini & Yamanaka, 2018; Soom et al., 1997; White, Bissiere, Alvarez, & Plachta, 2016). The ICM develops into the embryo and the trophectoderm forms extraembryonic structures including the placenta. Adhesion molecules have important functions starting from the initial stages of compaction through to implantation, and also in ongoing embryonic development (Barone & Heisenberg, 2012; Bloor et al., 2002; Fierro-Gonzalez, White, Silva, & Plachta, 2013; Fleming et al., 2001; Halbleib & Nelson, 2006; Kintner, 1992; Moore, Tao, Meng, Smith, & Xu, 2014; Nose & Takeichi, 1986; Pfeffer, 2018; Watson & Barcroft, 2001; White & Plachta, 2013). A series of studies, primarily using mouse and rat models, have led to the understanding that E-cadherin and N-cadherin are required for the development of normal embryos, while P-cadherin appears not to be required for early embryogenesis (Kan et al., 2007; Radice et al., 1997). Formation of the trophectoderm epithelium is the first adhesion-dependent differentiation in the developing embryo and is influenced by E-cadherin (Fleming et al., 2001; Marrs & Nelson, 1996; Shehu, Marsicano, Flechon, & Galli, 1996; Watson & Barcroft, 2001), although E-cadherin may not be obligatory (Filimonow et al., 2019). Mouse embryos with mutated E-cadherin that lacked Ca^{2+} binding had a disorganized morula shortly after compaction and failed to develop (Riethmacher, Brinkmann, & Birchmeier, 1995). In other E-cadherin mutation studies in mice, embryos showed compaction and developed into blastocysts but failed to form a trophectoderm (Kan et al., 2007; Larue, Ohsugi, Hirchenhain, & Kemler, 1994; Radice et al., 1997). In the latter studies, residual maternal (oocyte) E-cadherin was able to support some compaction but did not support the formation of a functional trophectoderm (Stephenson, Yamanaka, & Rossant, 2010; de Vries et al., 2004). Embryos that lack a properly constituted trophectoderm are unable to achieve implantation and do not develop.

The expression and distribution of E-cadherin were studied during the transition from the maternal to the embryonic genome using in vitro fertilization (IVF) embryos from adult and juvenile sheep (Modina et al., 2010). Embryos from adult sheep showed the expected expression and cellular distribution of E-cadherin, while embryos from juvenile sheep showed uneven distribution in disorganized blastomeres. It was suggested that the normal expression of E-cadherin is required for embryo organization and development in sheep (Modina et al., 2010). Embryos derived from previously vitrified sheep oocytes had altered expression of E-cadherin and showed poor development (Shirazi, Heidari, Shams-Esfandabadi, Momeni, & Derafshian, 2015). Vitrified buffalo embryos also showed altered expression of E-cadherin and β-catenin and had a low pregnancy rate (Moussa et al., 2019).

3.4 | Embryonic attachment and implantation

After hatching from the zona pellucida, trophoblasts interact with the extracellular matrix to move within the lumen of the uterus, and also with the uterine epithelium to achieve initial apposition (Sutherland, Calarco, & Damsky, 1988). Adhesion between the uterine endometrial epithelia and the trophectoderm epithelia is a prerequisite for attachment and implantation (Biggers, Bell, & Benos, 1988; Davidson & Coward, 2016; Figure 5).

Interaction of the trophoblast with both the extracellular matrix and uterine epithelium involves adhesion molecules (Lessey, 2002; van Mourik, Macklon, & Heijnen, 2009). Integrins are one of the predominant families of adhesion molecules present on the trophectoderm (Sutherland, Calarco, & Damsky, 1993). These integrins adhere to integrins expressed by the uterine epithelium (Bowen & Hunt, 2000; Bowen et al., 1996; Kang, Forbes, Carver, & Aplin, 2014; Figure 5). The interaction between trophoblast and uterine integrins appears to be facilitated by reduced expression of the antiadhesion protein MUC-1 at the point of trophoblast apposition with the uterus. This has been demonstrated for rodents, livestock, and primates (Aplin et al., 2001; Bowen et al., 1996; DeSouza, Mani, Julian & Carson, 1998; Hild-Petito, Fazleabas, Julian, & Carson, 1996; Spencer, Johnson, Bazer, & Burghardt, 2004; Figure 5).

Integrins interact with the extracellular matrix protein osteopontin (secreted phosphoprotein 1; Denhardt & Guo, 1993; Johnson, Burghardt, Bazer, & Spencer, 2003). It was proposed that osteopontin was the bridge that linked the integrin $\alpha_v\beta_6$ on the trophectoderm to $\alpha_v\beta_6$ on uterine luminal epithelial cells in pigs and sheep (Erikson, Burghardt, Bayless, & Johnson, 2009; Johnson, Burghardt, & Bazer, 2014; Johnson et al., 2001) and humans (Kang et al., 2014). It was also reported that osteopontin bound $\alpha_v\beta_3$ and $\alpha_5\beta_1$ on the trophectoderm to facilitate migration and attachment to the uterine epithelium in sheep (Kim et al., 2010). In one study, $\alpha_v\beta_6$ and osteopontin were found not to colocalize in trophoblasts and uterine epithelium in sheep and cattle, and it was concluded from this finding that these proteins may not always cooperate in embryo attachment in ruminants (Kimmins, Lim, & MacLaren, 2004).

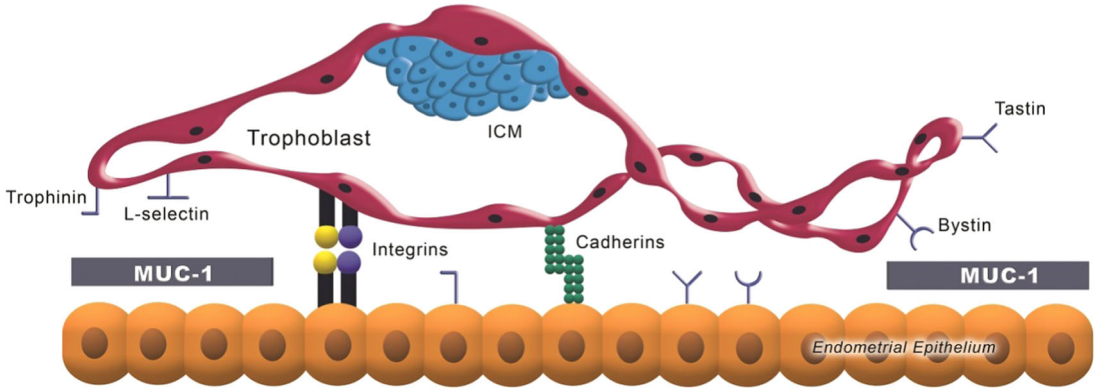

FIGURE 5 Diagrammatic representation of cell–cell adhesion molecules shown to be involved in initial attachment between the trophoblast and uterine endometrial epithelium. The families of adhesion molecules involved include cadherins, integrins, trophinins, L-selectins (Feng et al., 2017), bystins (Suzuki et al., 1998), and tastins (Bloor et al., 2002). Different adhesion molecules are thought to be involved in trophoblast–endometrium interaction in different species. The attachment exclusion molecule MUC-1 is not expressed in the segment of the endometrial epithelium where attachment of the trophoblast occurs. ICM, inner cell mass

Attachment of the trophectoderm to the uterine epithelia has received considerable attention in humans. One line of research suggests that E-cadherin is involved in initial adhesion between the trophoblast and uterus (Kokkinos et al., 2010). This is followed by the reduced expression of E-cadherin by epithelial cells and loosening of cell–cell adhesion within the epithelial layer. The latter allows the infiltration of the trophoblast and commencement of implantation (Aplin & Ruane, 2017; Coutifaris et al., 1991; Kokkinos et al., 2010). The second line of research in humans has proposed that the binding protein L-selectin is expressed by trophoblasts and interacts with its ligand on uterine epithelia (Feng et al., 2017; Fukuda & Sugihara, 2008; Genbacev et al., 2003; Lai et al., 2005). This is followed by attachment through the homotrophic (self-binding) adhesion molecule trophinin that is present on the trophoblast and uterine endometrial epithelia (Fukuda & Sugihara, 2008; Fukuda et al., 1995; Genbacev et al., 2003; Sugihara et al., 2007; Suzuki et al., 1999; Figure 5). Other adhesion molecules reported to have a role in trophoblast–endometrial cell adhesion in humans are bystin and tastin (Suzuki et al., 1999; Figure 5).

It can be concluded from the above that both within and between species, a range of adhesion molecules can be involved in the initial attachment of the trophoblast to the uterine epithelium. For example, annexin A1 and annexin A2 were reported to have a lesser expression in the chorioamnion and adjacent uterine caruncles for embryos with retarded development compared to embryos with normal development in the Italian Mediterranean River buffalo (Balestrieri et al., 2013; Strazzullo et al., 2014). Annexin A2 has been specifically implicated in embryo attachment in humans (Barone & Heisenberg, 2012; Garrido-Gomez et al., 2012) and mice (Wang et al., 2015), while annexin A1 is involved with general cell adhesion (Horlacher et al., 2011). The studies in River Buffalo provided a clear demonstration of altered adhesion molecule function in a well-characterized model of retarded embryonic development (Campanile, Neglia, & D'Occhio, 2016).

4 | ADHESION MOLECULES AND REPRODUCTION IN CATTLE

Fertilization rates in cattle are in the order of 85–90% but up to 40–50% of embryos do not result in a pregnancy (D'Occhio et al., 2019; Sponchiado et al., 2019). The low embryo survival in cattle provides a compelling reason for more research to better understand the biology of early reproductive events in cattle. Within the context of this review, studies in buffaloes (Moussa et al., 2019), pigs (Bowen et al., 1996), and sheep (Modina et al., 2010; Shirazi et al., 2015) have shown important roles for adhesion molecules in early embryonic development in livestock. It is known that Days 8–17, bovine embryos secrete interferon-tau (IFNT), which induces the expression of uterine IFNT-stimulated genes that are involved with implantation (D'Occhio et al., 2019). The argument is made in this review that the expression of adhesion molecules by the embryo and uterus is as equally important for the establishment of a pregnancy. This section looks at what is known for adhesion molecules and early reproductive events in cattle. Areas are identified where a deeper understanding of the role of adhesion molecules should lead to new strategies for improving embryonic survival. Cattle are the focus given their low embryo survival and importance in global food systems. A major improvement in reproductive efficiency in cattle would have biological significance and would also help to achieve production, social, and environmental objectives (D'Occhio et al., 2019).

Bovine oviduct epithelial cells in culture secreted the extracellular matrix protein fibronectin (Singh, Carraher, & Schwarzbauer, 2010) which attached to the integrin $\alpha_5\beta_1$, a fibronectin ligand, present on sperm (Osycka-Salut et al., 2017). It was proposed that fibronectin-sperm $\alpha_5\beta_1$ attachment is involved in sperm interaction with the oviduct which maintains sperm integrity before fertilization (Osycka-Salut et al., 2017). Fibronectin and $\alpha_5\beta_1$ were also reported to be expressed by bovine sperm and oocytes during IVF (Thys et al., 2009). This led to the suggestion that fibronectin acts as "velcro" to

facilitate initial sperm–oocyte attachment in cattle (Thys et al., 2009). In one study, bovine oocytes expressed a number of α-subunit and β-subunit integrins, further suggesting a role for integrins in sperm–oocyte interaction in cattle (Pate et al., 2007). An integrin ligand with the RGD (Arg-Gly-Asp) motif was found to induce parthenogenetic development in bovine oocytes (Campbell, Reed, & White, 2000). Single-nucleotide polymorphisms (SNPs) in the integrin β_5 gene (*ITGB5*) and extracellular matrix protein collagen Type 1 alpha 2 gene (*COL1A2*) were associated with fertility in bulls (Feugang et al., 2009). Also, integrin β_5 antibodies reduced the ability of bovine sperm to fertilize oocytes (Feugang et al., 2009). It can be concluded that integrins are involved in early functions of bovine gametes and in sperm–oocyte attachment. E-cadherin and β-catenin were also found to be expressed by bovine oviduct epithelial cells, sperm, and COCs, suggesting a role also for cadherins in sperm–oocyte attachment and fertilization in cattle (Caballero et al., 2014). ADAMs are additionally expressed on bovine sperm and can have a role in sperm–oocyte attachment (Waters & White, 1997). Osteopontin was located on bovine sperm and was proposed to bind integrins, and/or other binding molecules, on oocytes during initial sperm–oocyte attachment in cattle (Erikson, Way, Chapman, & Killian, 2007).

Bovine IVF embryos express E-cadherin and β-catenin. The expression is related to the stage of development (Barcroft et al., 1998; Shehu et al., 1996) and, in one study, expression was greater in good quality blastocysts compared to poor quality blastocysts (Sathanawongs, Nganvongpanit, & Mekchay, 2012). IFNT enhanced the development of bovine IVF embryos (Bao, Zhao, Haq, & Zeng, 2014; Zhao, Wu, Gao, Evans, & Zeng, 2017) and this was associated with upregulation of E-cadherin and connexin 43, the latter a gap junction intercellular communication protein (Ribeiro-Rodrigues et al., 2017). Suppression of the E-cadherin gene and connexin 43 gene using RNA interference decreased the proportion of bovine embryos that developed to blastocysts (Nganvongpanit et al., 2006; Tesfaye et al., 2007). The expression of E-cadherin and connexin 43 in bovine embryos was influenced by the culture system and whether embryos were produced in vivo or in vitro (Lonergan et al., 2003; Niemann & Wrenzycki, 1999; Wrenzycki, Herrmann, Carnwath, & Niemann, 1996, 1999; Wrenzycki, Herrmann et al., 2001). Bovine embryos produced by nuclear transfer had a similar relative abundance of E-cadherin messenger RNA as IVF embryos (Wrenzycki, Wells et al., 2001). Combined, these findings strongly suggest that E-cadherin is fundamental to embryonic development in cattle.

The trophectoderm of bovine embryos has a polarized epithelium that develops into mononucleated and binucleate cells (Barcroft et al., 1998; Igwebuike, 2006; Negron-Perez, 2017; Wooding, 1982; Wooding & Wathes, 1980). Bovine embryos express E-cadherin and β-catenin during binucleate cell differentiation (Barcroft et al., 1998; Nakano et al., 2002; Nakano, Shimada, Imai, Takahashi, & Hashizume, 2005). However, it has yet to be conclusively shown that the cadherin–catenin system is obligatory for this differentiation to take place in cattle embryos (Negron-Perez, 2017). The outgrowth of hatched bovine blastocysts was studied in cultures with the extracellular matrix proteins fibronectin, laminin, and vitronectin. All three matrix proteins supported outgrowth, apparently by acting as ligands for trophoblast integrins (Singleton & Menino, 2005; M. Takahashi, Takahashi, Hamano, Takahashi, & Okano, 2005). It was suggested that bovine endodermal cells can also use nonintegrin cell adhesion mechanisms during outgrowth (Singleton & Menino, 2005).

Binucleate cells of the trophectoderm epithelium are involved in the attachment of the elongating trophoblast to the uterine epithelium in cattle (Bowen & Burghardt, 2000; Wooding, 1992). A range of adhesion molecules and their ligands have been implicated in the process of attachment and implantation in cattle. These include ADAMs, E-cadherin and N-cadherin, vascular cell adhesion molecule, integrins and their ligands, selectins and their ligands, and extracellular matrix proteins (fibronectin, selectin; MacIntyre et al., 2002; Xiang & MacLaren, 2002; Sakurai et al., 2012; Bai et al., 2014, 2015; Imakawa & Kusama, 2018). The bovine uterine epithelium expresses integrins and the extracellular matrix proteins collagen IV and laminin during attachment and implantation (Kimmins & MacLaren, 1999; MacIntyre et al., 2002). In one study, however, the integrin $\alpha_v\beta_3$ was not expressed by bovine trophoblast, and $\alpha_v\beta_3$ and its ligand osteopontin did not colocalize in the bovine uterine epithelium (Kimmins et al., 2004). This led to the suggestion that $\alpha_v\beta_3$ may not be obligatory for trophoblast–uterine attachment in cattle. In this regard, IFNT stimulated the expression of E-cadherin and β-catenin in cultured bovine endometrial epithelial cells (Barragan, 2006).

Bovine embryos produced by somatic cell nuclear transfer (SCNT) had reduced amounts of E-cadherin and β-catenin proteins, and the corresponding cotyledons had altered localization of E-cadherin and β-catenin (Kohan-Ghadr, Smith, Arnold, Murphy, & Lefebvre, 2012). This was proposed as one explanation for inadequate placentation associated with bovine nuclear transfer embryos. In another study, genes associated with Ca^{2+} mobilization and trophoblast adhesion had different expression in uterine endometrium amongst bovine in vivo, IVF, and SCNT embryos (Mansouri-Attia et al., 2009). Uterine gene expression in cattle would appear to reflect the capacity of an embryo to attach, implant, and establish a pregnancy. Other studies in cattle have provided strong evidence that uterine gene expression differs between animals with inherently low and high fertility, which is independent of embryonic factors (McMillan & Donnison, 1999; Minten et al., 2013; Petersen & Lee, 2003). A major advance in embryonic survival in cattle could, therefore, include the identification and multiplication of females that have a genetic predisposition for an optimal uterine function to establish and maintain a pregnancy. Whole-genome association studies have an important application in identifying SNPs for embryo survival and pregnancy in cattle. For example, SNPs in the L-selectin gene cluster were associated with fertility and longevity in Holstein Friesian cows (X. Chen et al., 2017). In a recent study in female Brahman and Nellore cattle (de Melo, Fortes, Hayes, de Albuquerque, & Carvalheiro, 2019), SNPs associated with fertility were linked with blastocyst development (genes *GCGN*, *ATF6B*; Gad et al., 2011), embryonic development (genes *NF1B*, *NAPA*, *ZPR1*, *TAF8*, *HEX1M1*, *HEX1M2*; Mamo et al., 2011; Al Naib, Mamo, & Lonergan, 2012),

uterine function (genes *C11H2orf49*, *CCND3*; Hayashi et al., 2017), and general cell proliferation and morphogenesis (gene *CHSY1*; Becker-Santos, Lonergan, Gronostajski, & Lam, 2017). While the study of de Melo et al. (2019) did not specifically address adhesion molecules it did illustrates the importance of early reproductive events in determining reproductive outcome. Within the context of the present review, it can be assumed that differences in conceptus and uterine function linked to SNPs would impact on adhesion molecules as a part of the broader picture of factors that influence embryo survival, implantation, and pregnancy in cattle.

It will be important to establish clearer roles for adhesion molecules in sperm–oocyte interaction, embryonic development, and embryonic attachment and implantation in cattle. This will require standardized, systematic, and well-designed and executed studies. The current literature is limited by recurring discrepancies that, in part, reflect research bias and poor design. The case is made in this review that major advances in the efficiency of natural mating and assisted breeding in cattle will depend on a deeper understanding of the cellular and molecular mechanisms that support early reproductive events. Particularly important will be a greater understanding of the role of adhesion molecules. An appropriate balance of discovery and applied research is needed. With regard the latter, the increasing use of assisted reproductive technology in cattle provides the opportunity for rapid application of new knowledge of gametes and embryos.

5 | CONCLUSION AND PERSPECTIVES

The action of adhesion molecules in cell–cell contact and cell signaling during cellular movement and in shaping tissues merges with the field of mechanobiology or mechanotransduction (Hoffman & Yap, 2015; Sun, Guo, & Fassler, 2016). This brings together biology and physical forces that operate in cellular systems (Leckband & de Rooij, 2014), and is particularly relevant to the functions of gametes and embryos. It is abundantly clear that adhesion molecules have important roles in gamete transport, sperm–oocyte interaction, embryonic development, and implantation. Less clear are the specific families of adhesion molecules and extracellular matrix proteins involved at each phase of early reproductive events. This is partly the result of species differences but it is also due to different emphases and experimental approaches across studies. The reader would have noted that many of the cited papers were published in the late 1900s and early 2000s. Research in the field has tended to move to cancer biology with less activity in reproduction. This could be partly due to the ability to secure funding in different fields of science. Whatever the reasons, adhesion molecules seem to be largely overlooked when considering reproductive mechanisms. This needs to be addressed given the fundamental roles for adhesion molecules presented in this review. A strong case can be made that a renewed emphasis on adhesion molecules and reproduction, combined with enabling technology platforms (e.g., assisted reproductive technology, genomics), will provide new insight into reproductive mechanisms (Matsumoto, 2017). In turn, this will inform new strategies to improve the efficiency of natural mating and assisted breeding in mammals.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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