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Review

Involvement of gap junctions in placental functions and development

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Abstract

Connexin (Cx) expression and gap junctional intercellular communication (GJIC) are involved in development and differentiation processes. Mediating exchanges between mother and fetus, the placenta is formed when fetal membranes are apposed or even fusing or destroying the uterine mucosa. Therefore, an extraordinary variability of placental structures is observed throughout the mammalian species. This variability affect mainly, the maternofetal blood flow interrelationships, the kind and number of tissue layers separating maternal and fetal bloods, the trophoblast invasiveness and the formation of a syncytium (syncytiotrophoblast). Here, the expression, the localisation and the possible role of Cx and GJIC in placental functions and development are discussed. In rodents, gene knock out in mice have vastly improved our understanding of the role of Cx genes in mouse placental development: Cx26 in transplacental uptake of glucose, Cx31 in the proliferative process of trophoblastic cells and Cx45 in placental vascularisation. In human, it appears that Cx43 allows a GJIC required for the fusion process of cytotrophoblastic cells leading to the formation of the syncytiotrophoblast, the site of the numerous placental functions. On other hands, Cx40 plays a critical role in the switch from a proliferative to an invasive phenotype of the trophoblastic cells invading the endometrium. Owing to the striking diversity of Cx expression in placental structures, we must be careful when extrapolating findings from one species to another.

Keywords: Gap junction; Placenta; Trophoblast; Connexin; Cell–cell communication; Differentiation process

Contents

1. Introduction

Gap junctions are clusters of transmembrane channels composed of connexin (Cx) dodecamers that mediate cell-to-cell communication in almost tissues. In mammals, gap junction channels are composed of two hemi-channels termed connexons, each provides by one of the two neighbouring cells and tightly associated in the intercellular space. In general,

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effects of Cx have been attributed to gap junctional intercellular communication (GJIC) and sharing a common pool of intracellular messengers and metabolites. Gap junctions provide a pathway for the diffusion of ions and small molecules such as cAMP, cGMP, inositol triphosphate (IP3) and Ca^{++}. Connexins represent a family of closely related membrane proteins, which are encoded by a multigene family that contains at least 20 members in human. All represent structurally conserved non-glycosyled transmembrane proteins, 25 to 62 kDa in size, that differ chiefly in the length of their C-terminal domain. Biophysical and functional properties of the intercellular channels depend on the type of connexins expressed. However, it is important to note that a specific function cannot be associated with one specific connexin. Although each connexin isoform exhibits a distinct tissue distribution, many cell types express more than one connexin [1]. The permeability of junctional channels is finely regulated: cAMP, Ca^{++} intracellular levels, pH, phosphorylation, transjunctional applied voltage [2]. In addition, the gap junction biosynthesis is a highly complex process and the delivery, assembly and removal of gap junctional channels appears to be an independent mechanism to control the GJIC [3]. Furthermore, secondary proteins interacting with connexins have been identified: chaperones, scaffolding proteins, kinases, phosphatases, cell signalling molecules [4]. These molecules will undoubtedly aid the multiple steps of gap junction channels.

Connexin expression varies during differentiation, proliferation and transformation processes and following treatment with biologically active substances such as growth factors and hormones [5–8]. The main effects of Cx expression have been attributed to GJIC [9] and to the interaction of connexin with the intracellular signal cascade via the carboxy-terminus [4].

In mammals, the blastocyst defines with the maternal organism by an implantation process a structure which allows the development of the embryo and the fetus: the placenta. This organ is formed when the fetal membranes surrounding the fetus are apposed or even fusing or destroying the uterine mucosa. The placenta is unique among other organs in that it possess the functional activities of other organs: gas and metabolic transfer, excretion, endocrine and immunological activities. To succeed these functions, an extraordinary variability of placental structures has been developed throughout the mammalian species. This variability affect mainly, the maternofetal blood flow interrelationships, the kind and number of tissue layers separating maternal and fetal bloods, the trophoblast invasiveness and the formation of a syncytium (syncytiotrophoblast) [10].

In this review, the expression, the localisation and the possible role of connexins and of GJIC in placental functions and development of the various placental types will be discussed (Table 1).

2. Epithelio and synepitheliochorial placentae

In the epitheliochorial placenta, the blastocyst did not invade the endometrium, subsequently, the fetal chorion

Table 1
Connexin expression in the various placental types

Placental type	Cell type	Connexin expression	Function	References
Epitheliochorial				
Horse	Stromal cells	Cx43		[11]
Pig	Stromal cells	Cx43		[11]
Synepitheliochorial				
Sheep	Stromal cells	Cx43		[12]
	Uterine epithelial cells	Cx26		[12]
Cow	Maternal and fetal mesenchyme	Cx43		[13]
	Uterine epithelial cells	Cx32		[13]
		Cx26		
	Trophoblastic giant cells	Cx26	Migration/fusion?	[13]
		Cx43		
Hemochorial				
Rat	Syncytiotrophoblastic Layer I and II	Cx26	Transfer	[20]
	Trophoblastic cells ectoplacental cone	Cx31		[19]
	Spongiotrophoblast	Cx43		[19]
	Trophoblastic giant cells	Cx43		[19]
Mouse	Syncytiotrophoblastic Layer I and II	Cx26		[21]
	Trophoblastic cells ectoplacental cone	Cx31	Cell proliferation	[25,27]
	Spongiotrophoblast	Cx43		
	Trophoblastic giant cells	Cx43		[23]
Human	*Villous trophoblast*			
	Cyto- and syncytiotrophoblast	Cx43	Cell fusion	[33,34,36,37]
	Fetal mesenchyme	Cx43		
	Extravillous trophoblast			
	Proximal proliferative cells of the column	Cx40	Cell proliferation	[34,44]
	Trophoblastic aggregated cells of the placental bed	Cx43	Cell fusion	[42]
		Cx32		