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The Immunobiology of Preterm Labor and Birth: Intra-Amniotic Inflammation or Breakdown of Maternal-Fetal Homeostasis

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Author contribution statement

N.G.-L. conceptualized the manuscript and supervised the study. N.G.-L., J.G., D.M., M.F.-J., Z.L., M.A.-H., V.G.-F., Z.S., J.G., K.R.T., and R.R. drafted and revised the manuscript, performed literature review, created figures, and/or provided intellectual input. All authors approved the final version of the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Abstract

Preterm birth, the leading cause of neonatal morbidity and mortality worldwide, results from preterm labor, a syndrome that includes multiple etiologies. In this review, we have summarized the immune mechanisms implicated in intra-amniotic inflammation, the best-characterized cause of preterm labor and birth. While the intra-amniotic inflammatory responses driven by microbes (infection) or alarmins (sterile) have some overlap in the participating cellular and molecular processes, the distinct natures of these two conditions necessitate the implementation of specific approaches to prevent adverse pregnancy and neonatal outcomes. Intra-amniotic infection can be treated using the correct antibiotics, whereas sterile intra-amniotic inflammation could potentially be treated using a combination of anti-inflammatory drugs (e.g., betamethasone, inflammasome inhibitors, etc.). Recent evidence also supports a role for fetal T-cell activation as a newly described trigger for preterm labor and birth in a subset of cases. Moreover, here we also provide evidence of two potential immune mechanisms responsible for a subset of preterm births formerly considered to be idiopathic. First, the impairment of maternal Tregs can lead to preterm birth, likely due to the loss of immunosuppressive activity resulting in unleashed effector T-cell responses. Second, homeostatic macrophages were shown to be essential for maintaining pregnancy and promoting fetal development, and the adoptive transfer of homeostatic M2-polarized macrophages shows great promise for preventing inflammation-induced preterm birth. Collectively, in this review, we discuss established and novel immune mechanisms responsible for preterm birth and highlight potential targets for novel strategies aimed at preventing the multi-etiological syndrome of preterm labor.

In brief:

The syndrome of preterm labor comprises multiple established and novel etiologies. This review summarizes the distinct immune mechanisms implicated in preterm labor and birth and highlights potential strategies for its prevention.

Introduction

Preterm birth affects over 15 million pregnancies annually and remains a leading cause of neonatal morbidity and mortality (Liu et al., 2015, Chawanpaiboon et al., 2019). In addition to its drastic short-term consequences, preterm birth can have lasting effects on development that can persist into adulthood (Abitbol and Rodriguez, 2012, Carmody and Charlton, 2013, O'Reilly et al., 2013, Blencowe et al., 2013, Ream and Lehwald, 2018). Preterm deliveries are largely spontaneous, with the remainder being iatrogenic (i.e., medically indicated) (Goldenberg et al., 2008, Romero et al., 2014a). Spontaneous preterm birth results from preterm labor, a syndrome that includes multiple causal and associated etiologies (Romero et al., 2014a). Among these, inflammation of the amniotic cavity (i.e., intra-amniotic inflammation) is the most well-established cause (Romero et al., 2006b, Romero et al., 2007, Goldenberg et al., 2008, Romero et al., 2014a). Intra-amniotic inflammation can

occur in two different contexts: the first results from the invasion of the amniotic cavity by microbes, termed intra-amniotic infection, whereas the second takes place in the absence of microbes and is associated with an increase in endogenous danger signals or alarmins, termed sterile intra-amniotic inflammation (Romero et al., 2006b, Romero et al., 2007, Goldenberg et al., 2008, Romero et al., 2014a, Romero et al., 2014b, Romero et al., 2014c, Romero et al., 2015b, Romero et al., 2015c). Importantly, a growing body of evidence has indicated that, although these two inflammatory states have similar clinical outcomes, they are intrinsically distinct from one another (Romero et al., 2014c, Romero et al., 2015a, Bhatti et al., 2020, Motomura et al., 2021a). Therefore, understanding the differences between the pathogenesis of intra-amniotic infection and sterile intra-amniotic inflammation is essential for determining the correct patient management.

A large proportion of spontaneous preterm births, however, are not associated with inflammation of the amniotic cavity and fetus (whether microbial or sterile), and have thus been grouped into the broad category of idiopathic preterm birth (Goldenberg et al., 2008, Barros et al., 2015). Among the proposed causes of idiopathic preterm birth, a breakdown of maternal-fetal tolerance has been put forward as a potential trigger for maternal inflammatory responses leading to the onset of preterm labor (Romero et al., 2014a). Pregnancy represents a tightly controlled maternal immune response that requires a delicate balance between effective host defense against potential infection (Bizargity et al., 2009, Arenas-Hernandez et al., 2016, van Egmond et al., 2016, van der Zwan et al., 2018) and maintaining tolerance of the foreign conceptus (Aluvihare et al., 2004, Taglauer et al., 2010, Munoz-Suano et al., 2011, Mold and McCune, 2012, Arck and Hecher, 2013, Erlebacher, 2013). Moreover, recent evidence has suggested that the fetus itself can exhibit immune responses and must therefore also tolerate the mother (Mold et al., 2008, Ivarsson et al., 2013, McGovern et al., 2017, Frascoli et al., 2018), given that fetal T-cell activation is associated with preterm labor and birth (Frascoli et al., 2018, Gomez-Lopez et al., 2019g). Such bidirectional tolerance is therefore the result of complex immunological adaptations that occur both systemically and locally (i.e., at the maternal-fetal interface), of which the latter involves both innate and adaptive cellular immune components (Croy et al., 1985, Aluvihare et al., 2004, Sasaki et al., 2004, Houser et al., 2011, Svensson et al., 2011, Bartmann et al., 2014, Vacca et al., 2015, Doisne et al., 2015, St Louis et al., 2016, Xu et al., 2016, Gomez-Lopez et al., 2017a, Xu et al., 2018b, Miller et al., 2018, Jiang et al., 2018, Vazquez et al., 2019, Arenas-Hernandez et al., 2019, Leng et al., 2019, Salvany-Celades et al., 2019, Gomez-Lopez et al., 2020, Gomez-Lopez et al., 2021a). In particular, regulatory T cells (Tregs) are considered important antigen-specific mediators of maternal-fetal tolerance through their suppression of potentially harmful effector T-cell responses (Zenclussen et al., 2005, Darrasse-Jèze et al., 2006, Kahn and Baltimore, 2010, Shima et al., 2010, Rowe et al., 2011, Samstein et al., 2012, Rowe et al., 2012, Chen et al., 2013, Diao et al., 2021), and thus the dysfunction of these cells has been implicated in preterm birth (Schober et al., 2012, Gomez-Lopez et al., 2020). Indeed, we recently provided mechanistic evidence supporting a critical role for Tregs in late pregnancy by demonstrating that the loss of these cells leads to preterm birth in mice (Gomez-Lopez et al., 2020). However, Treg dysfunction/deficiency only seems to be responsible for a small subset of preterm births (Gomez-Lopez et al., 2020); thus, we reasoned that other immune cells are

contributing to maternal-fetal tolerance and may therefore be implicated in a breakdown of this process leading to preterm birth. Macrophages are considered to be important for preserving immune homeostasis at the maternal-fetal interface (Hunt et al., 1984, Gustafsson et al., 2008, Svensson et al., 2011, Svensson-Arvelund et al., 2015, Svensson-Arvelund and Ernerudh, 2015, Chambers et al., 2020, Abassi et al., 2020, Gomez-Lopez et al., 2021a); however, the importance of these cells in late pregnancy had not yet been demonstrated. Using an animal model of macrophage depletion, we showed that the loss of these cells in late gestation resulted in preterm birth as well as neonatal mortality (Gomez-Lopez et al., 2021a). Importantly, we also showed that the restoration of homeostatic macrophages could prevent inflammation-associated preterm birth and adverse neonatal outcomes in mice, further demonstrating the importance of these cells for pregnancy maintenance (Gomez-Lopez et al., 2021a). Therefore, deciphering the contributions of these immune cell subsets to successful pregnancy may allow for the identification of novel approaches that can be used to prevent preterm labor and birth.

In this review, we first discuss the discovery, clinical definitions, and immune mechanisms implicated in intra-amniotic infection and sterile intra-amniotic inflammation. Moreover, we discuss the current and potential approaches that can be used to treat these two distinct clinical conditions. Next, we discuss the activation of the fetal immune system as a novel mechanism leading to preterm birth. We then focus on the mechanisms whereby maternal effector T cells, Tregs, and macrophages participate in successful pregnancy. In addition, we review the evidence implicating each subset in the pathophysiology of preterm labor and birth, and potential therapeutic approaches that can be used to target these cells. We aim to provide an overview of key immunological processes implicated in preterm labor and birth, which can provide deeper understanding, highlight gaps in knowledge, and provide potential targets for future therapies that can be used to treat this devastating obstetrical syndrome.

Intra-amniotic infection: the most well-known etiology of preterm labor and birth

The amniotic cavity has been classically thought to be a sterile compartment (Perez-Munoz et al., 2017), and therefore the detection of viable microorganisms in the amniotic fluid is considered to be abnormal. Microbial invasion of the amniotic cavity (MIAC) can elicit a local inflammatory response (i.e., microbial-associated intra-amniotic inflammation) (Naeye and Ross, 1982, Romero et al., 1991b, Romero et al., 1993c, Martinez-Varea et al., 2017, Gomez-Lopez et al., 2018c, Gomez-Lopez et al., 2019b, Galaz et al., 2020c, Galaz et al., 2020a). Microbial-associated intra-amniotic inflammation, referred to hereafter as intra-amniotic infection, is defined as the presence of microbes together with intra-amniotic inflammation [i.e., increased concentrations of IL-6 or MMP-8 (Park et al., 2001, Yoon et al., 2001)] (Goldenberg et al., 2008, Romero et al., 2014a, Romero et al., 2014b, Romero et al., 2014c, Romero et al., 2015b, Romero et al., 2015c), and is strongly associated with preterm labor and delivery (Romero et al., 2001, Goncalves et al., 2002, Goldenberg et al., 2008, Bastek et al., 2011, Romero et al., 2014a). Although a small subset of patients with intra-amniotic infection may progress to a systemic maternal infection (i.e., clinical chorioamnionitis (Gibbs et al., 1982, Gibbs and Duff, 1991)), the majority of women with

intra-amniotic infection/inflammation are asymptomatic, supporting the subclinical nature of this condition (Gravett et al., 1986, Gibbs et al., 1992, Romero et al., 2006a, Romero et al., 2007, Goldenberg et al., 2008). Notably, microbiological analyses of the amniotic fluid suggest that approximately 25% of all spontaneous preterm births are related to infection (Gibbs et al., 1992, Romero et al., 2001, Goncalves et al., 2002, Goldenberg et al., 2008, Romero et al., 2014a). The proportion of patients with intra-amniotic infection is variable among the different clinical obstetric scenarios. On average, the rate of positive amniotic fluid culture among numerous studies analyzing women with preterm labor and intact membranes is approximately 10% (Goncalves et al., 2002), and this rate is increased to over 20% among those who ultimately deliver preterm (Romero et al., 1989c). Among the studies of women with preterm prelabor rupture of membranes (PPROM), the mean rate of a positive amniotic fluid culture is about 30% at time of admission (Romero et al., 1988b, Goncalves et al., 2002, Romero et al., 2015b) and can reach up to 75% if the sample is collected at labor onset (Romero et al., 1988b). Furthermore, it has been shown using molecular microbiological techniques that a significant proportion of patients with PPROM who presented a negative amniotic fluid culture with intra-amniotic inflammation yielded a positive bacterial signal (DiGiulio et al., 2010, Romero et al., 2015b, Theis et al., 2020), suggesting the presence of non-cultivable microorganisms. Intra-amniotic infection is also present in up to 50% of women with cervical insufficiency (Romero et al., 1992a, Lee et al., 2008, Bujold et al., 2008, Oh et al., 2010, Lisonkova et al., 2014), as well as in one out of ten women with a sonographic short cervix (Hassan et al., 2006, Romero et al., 2015c). Although it is well known that a short cervix is considered a powerful predictor of preterm birth (Andersen et al., 1990, Iams et al., 1996, Heath et al., 1998, Berghella et al., 1999, Hassan et al., 2000, Romero, 2007, Rosenbloom et al., 2020, Gudicha et al., 2021), the presence of intra-amniotic infection among these patients confers an increased risk of early preterm delivery (i.e., before 34 weeks) compared to those without infection (Hassan et al., 2006, Romero et al., 2015c). Importantly, intra-amniotic infection is also associated with adverse neonatal outcomes, including increased morbidity and mortality (Yoon et al., 1996a, Yoon et al., 1999, Yoon et al., 2000b, Berger et al., 2004, Kirchner et al., 2007). Taken together, a large body of clinical evidence has implicated intra-amniotic infection as being strongly linked to spontaneous preterm labor and birth, thereby increasing the already high basal risk in a subset of women, including those with a short cervix.

To establish a causal link between intra-amniotic infection and preterm birth, multiple experimental approaches using animal models have been widely utilized (Dombroski et al., 1990, Gravett et al., 1994, Fidel et al., 2003, Novy et al., 2009, Boldenow et al., 2016, Gomez-Lopez et al., 2018a, Garcia-Flores et al., 2018, Faro et al., 2019, Motomura et al., 2020b). The intra-amniotic administration of microorganisms or their products (e.g., lipopolysaccharide or LPS) has been shown to induce preterm labor and birth in different animal models (Dombroski et al., 1990, Gravett et al., 1994, Fidel et al., 2003, Elovitz and Mrinalini, 2004, Novy et al., 2009, Boldenow et al., 2016, Gomez-Lopez et al., 2018a, Garcia-Flores et al., 2018, Faro et al., 2019, Motomura et al., 2020b, Stranik et al., 2020, Cappelletti et al., 2021). By comparing different routes of LPS administration (intra-amniotic, intra-uterine, and intra-peritoneal), we showed that only the intra-amniotic injection of this bacterial product resembles the subclinical nature of intra-amniotic

inflammation/infection (Gomez-Lopez et al., 2018a), in which the activation of the common pathway of labor typically occurs in the absence of systemic symptoms such as fever (Gravett et al., 1986, Romero et al., 1988b, Romero et al., 1989c, Gibbs et al., 1992, Romero et al., 2006a, Romero et al., 2007, Goldenberg et al., 2008). Therefore, a causal link between the presence of microorganisms or their products in the amniotic cavity and the onset of preterm labor was established.

How do microorganisms invade the amniotic cavity? Multiple routes have been proposed whereby microorganisms can reach the intra-amniotic space: 1) ascension from the lower genital tract; 2) hematogenous dissemination through the placenta (transplacental infection); 3) retrograde seeding from the peritoneal cavity through the fallopian tubes; and 4) accidental inoculation (i.e., iatrogenic) at the time of invasive procedures such as amniocentesis, cordocentesis, or chorionic villous sampling. A large number of investigations support the ascending route as the most common pathway of intrauterine infection (Romero et al., 1989c, Romero et al., 1990b, Romero et al., 2019, Oh et al., 2019a). Indeed, we recently investigated the bacterial profiles of amniotic fluids and vaginal swabs taken at the time of amniocentesis in women with intra-amniotic infection using conventional culture, matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF), and 16S ribosomal RNA (rRNA) gene sequencing (Romero et al., 2019). We found that the bacterial profiles of amniotic fluid are largely consistent with those of the vagina, thus generating solid evidence supporting the ascending route of microbial invasion of the amniotic cavity (Romero et al., 2019). Moreover, animal models have demonstrated the biological plausibility of ascending intra-amniotic infection (Vornhagen et al., 2016, Suff et al., 2018, Pavlidis et al., 2020, Gilbert et al., 2021, Spencer et al., 2021). The most common microorganisms cultured from the amniotic fluid of women with intra-amniotic infection include *Ureaplasma* spp., *Mycoplasma hominis*, *Gardnerella vaginalis*, and *Streptococcus agalactiae*, among others (Romero et al., 1989c, Yoon et al., 1998, DiGiulio et al., 2010, Mendz et al., 2013, Romero et al., 2014c, Romero et al., 2015d), all of which can be found in the vagina (Romero et al., 1989c, Romero et al., 2019). Additional evidence in favor of an ascending model of intra-amniotic infection comes from the demonstration of greater signs of inflammation/infection in tissues near the cervix. For example, histological inflammation is more common and severe in the cervical zone of the chorioamniotic membranes (Malak and Bell, 1994, McLaren et al., 1999, El Khwad et al., 2005, Nhan-Chang et al., 2010, Gomez-Lopez et al., 2011, Elfayomy and Almasry, 2014, Marcellin et al., 2017). Similarly, intra-amniotic inflammation is more prevalent in the first (i.e., closer to the cervix) rather than the second fetus in twin pregnancies affected by preterm labor with intact membranes (Romero et al., 1990b, Oh et al., 2019a). Thus, a four-stage ascending process of intrauterine infection from the lower genital tract has been classically proposed (Romero et al., 1988a, Goncalves et al., 2002). This process includes an initial alteration of the vaginal microbiome, characterized by a reduction in the proportion of commensal bacteria such as *Lactobacillus spp.* and the abnormal growth of pathological organisms (e.g., *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma parvum, Mycoplasma,* and *Gardnerella vaginalis*, among others) (stage I). Then, these pathological microorganisms gain access to the intrauterine cavity (stage II), causing a localized inflammatory reaction in the decidua and chorion. Here, the microorganisms

invade the amniotic cavity through the chorionic vessels or by directly crossing the intact membranes (stage III). Lastly, microorganisms in the amniotic cavity gain access to the fetus through different routes of entry, including the fetal mucosal tissues or the invasion of the fetal villous circulation (stage IV). A systemic dissemination of microbes from these fetal sites can occur, leading to fetal inflammatory response syndrome (FIRS) (Gomez et al., 1998, Romero et al., 1998, Pacora et al., 2002, Madsen-Bouterse et al., 2010, Jung et al., 2020, Para et al., 2021). Such fetal compromise may explain the increased risk of short- and long-term complications as well as death in neonates born to women with intra-amniotic infection (Yoon et al., 1998, Hitti et al., 2001, Yoon et al., 2003, Berger et al., 2004, Kirchner et al., 2007, Arayici et al., 2014, Kostlin-Gille et al., 2021).

In addition to the classical ascending route of intra-amniotic infection, the invasion of the amniotic cavity can also be caused by trans-placental infection in a small fraction of patients (Romero et al., 1989c, Goldenberg et al., 2008). Furthermore, maternal infections such as urinary tract infections (Kass, 1962, Romero et al., 1989b, Wing et al., 2014) and malaria (Menendez et al., 2000, Desai et al., 2007), among others (Kourtis et al., 2014, Fouks et al., 2018), have been associated with preterm labor and birth. Interestingly, molecular tools for bacterial detection in amniotic fluid have been useful to show the presence of microorganisms normally found in the oral cavity (e.g. *Fusobacterium nucleatum* and *Streptococcus* spp.) in pregnant patients at term (Bearfield et al., 2002), further supporting the proposed relationship between periodontal disease and adverse pregnancy outcomes through hematogenous dissemination (Goepfert et al., 2004, Le et al., 2021, Uwambaye et al., 2021). Collectively, these findings suggest that maternal bacteremia and trans-placental passage could account for some cases of intra-amniotic infection. However, additional research is required to establish a direct link between extra-uterine infectious conditions and spontaneous preterm labor and birth.

Host immune defense mechanisms in intra-amniotic infection

Once microbes have entered the amniotic cavity, different local and systemic mechanisms of host immune defense are elicited in both the maternal and the fetal compartments (Romero et al., 1989c, Gibbs and Duff, 1991, Romero et al., 2006a, Lee et al., 2006, Romero et al., 2007, Lee et al., 2007, Gotsch et al., 2007, Romero et al., 2014a). The local inflammatory response towards microbes invading the amniotic cavity is characterized by an infiltration of leukocytes, including both innate and adaptive immune cells (Romero et al., 1991b, Romero et al., 1993c, Gomez et al., 1994, Yoon et al., 1996b, Martinez-Varea et al., 2017, Gomez-Lopez et al., 2018c, Gomez-Lopez et al., 2019b, Galaz et al., 2020c, Galaz et al., 2020a, Galaz et al., 2020b, Gomez-Lopez et al., 2021c), as well as increased amniotic fluid concentrations of cytokines, chemokines and prostaglandins (Romero et al., 1986, Saito et al., 1993, Romero et al., 1993b, Hsu et al., 1998a, Hsu et al., 1998b, Yoon et al., 2001, Figueroa et al., 2005, Cobo et al., 2014, Park et al., 2016, Tarca et al., 2017, Peiris et al., 2020, Bhatti et al., 2020, McCartney et al., 2021, Peiris et al., 2021). Immunophenotyping of the cellular component of this immune response in patients with intra-amniotic infection has revealed that the most common cells involved in the local inflammatory response are neutrophils and monocytes/macrophages, as well as to a lesser extent T cells, B cells, and NK cells (Martinez-Varea et al., 2017, Gomez-Lopez et al., 2018c, Gomez-Lopez et al.,

2019g, Galaz et al., 2020a, Galaz et al., 2020c). Using DNA fingerprinting and fluorescence *in situ* hybridization, we have shown that both fetal and maternal neutrophils can access the amniotic cavity and participate in host defense against intra-amniotic infection/inflammation (Gomez-Lopez et al., 2017f). Similarly, monocytes/macrophages present in the amniotic fluid of patients with demonstrated infection/inflammation can originate from both the mother and the fetus (Gomez-Lopez et al., 2019d). However, in cases of intra-amniotic infection leading to preterm labor and birth, the majority of neutrophils and monocytes/macrophages in the amniotic fluid are derived from the fetus (Sampson et al., 1997, Gomez-Lopez et al., 2017f, Gomez-Lopez et al., 2019d). By contrast, a predominant maternal origin has been shown for neutrophils (Gomez-Lopez et al., 2017f) and monocytes/macrophages (Gomez-Lopez et al., 2019d) detected in the amniotic fluid of women with intra-amniotic infection/inflammation who delivered at term. Therefore, both the mother and fetus can display a local immune response to microbes in the amniotic cavity.

The immune response towards microbes invading the amniotic cavity requires the orchestration of multiple leukocyte functions. As first responders to infection, neutrophils are characterized by a variety of host defense mechanisms, including phagocytic capacity, the release of antimicrobial products and immune mediators, and the formation of neutrophil extracellular traps (NETs) (Mantovani et al., 2011, Burn et al., 2021). NETs are web-like structures composed of DNA, histones, and antimicrobial products such as neutrophil elastase that can trap microbes (Brinkmann et al., 2004, Fuchs et al., 2007, Brinkmann and Zychlinsky, 2012). Notably, we and others have demonstrated that neutrophils in amniotic fluid are capable of performing the abovementioned host defense mechanisms including phagocytosis (Gomez-Lopez et al., 2017b), release of antimicrobial products and immune mediators such as lactoferrin, defensins, tumor necrosis factor (TNF)-α and macrophage inflammatory protein-1β (Heller et al., 1995, Otsuki et al., 1999, Pacora et al., 2000a, Maymon et al., 2001, Espinoza et al., 2003, Gravett et al., 2004, Soto et al., 2007, Martinez-Varea et al., 2017, Varrey et al., 2018, Para et al., 2020), and formation of NETs (Gomez-Lopez et al., 2017g, Galaz et al., 2020c). Similarly, neutrophils infiltrating the chorioamniotic membranes in response to intra-amniotic infection also have the capacity to form NETs (Boldenow et al., 2016, Gomez-Lopez et al., 2017c, Tong et al., 2019, Tong et al., 2021). On the other hand, one of the primary functions of monocytes/macrophages is the production and secretion of pro-inflammatory cytokines (Serbina et al., 2008), which is consistent with reports of such cells expressing interleukin (IL)-1β and IL-1α in the amniotic cavity of patients with intra-amniotic infection (Martinez-Varea et al., 2017, Galaz et al., 2020c). Consistent with these distinct roles of neutrophils and monocytes/macrophages in intra-amniotic infection, high-throughput RNA sequencing analysis revealed differing transcriptomic profiles in these cell types (Gomez-Lopez et al., 2021c), thus highlighting the complexity of the local cellular innate immune responses in women with intra-amniotic infection. In addition, the inflammatory mediators detected in the amniotic fluid are mainly related to innate immune cells (i.e., neutrophils and monocyte/macrophages) (Gomez-Lopez et al., 2019b, Galaz et al., 2020a). Although the number of amniotic fluid T and B cells is also increased in patients with intra-amniotic infection/inflammation (Gomez-Lopez et al., 2018c), their contribution to the integrated immune response remains less clear, given the overwhelming presence of innate immune cells. Yet,

we recently proposed a role for the T-cell cytokine IL-22 in the host response against microbes invading the amniotic cavity by demonstrating the participation of this cytokine in the intra-amniotic inflammatory milieu that occurs prior to *Ureaplasma parvum*-induced preterm birth in mice, which was prevented by IL-22 deficiency (Gershater et al., 2022, Accepted). Thus, the cellular immune response of women at risk for spontaneous preterm birth with demonstrated intra-amniotic infection is greater than in those without infection, and is primarily driven by neutrophils, monocytes/macrophages, and, to a lesser extent, T cells (Fig. 1A).

Treatment of intra-amniotic infection

Considering the above demonstrations showing a strong relationship between intra-amniotic infection and spontaneous preterm birth as well as its adverse consequences, numerous randomized clinical trials have attempted to manage such risks using antibiotic therapy. Multiple clinical trials in patients with PPROM indicated that antibiotic therapy is associated with a longer latency period (time between the onset of PPROM and delivery) as well as reduced rates of clinical chorioamnionitis and neonatal sepsis (Mercer and Arheart, 1995, Kenyon et al., 2001a, Kenyon et al., 2013). Thus, antibiotics are considered a standard of care for women with PPROM (Ehrenberg and Mercer, 2001, Yudin et al., 2009, Thomson et al., 2019, American College of Obstetricians and Gynecologists, 2020). However, most studies evaluating the potential usefulness of antibiotics to prolong gestational length and reduce neonatal morbidity in women with preterm labor and intact membranes have been unsuccessful (Newton et al., 1989, Romero et al., 1993a, Gordon et al., 1995, Kenyon et al., 2001b). Such disparity in the success of antibiotic treatment could be explained by the greater prevalence of intra-amniotic infection in women with PPROM compared to those with preterm labor and intact membranes (Goncalves et al., 2002), and thus the benefits of antibiotics lies in their inherent function of killing bacteria or inhibiting bacterial growth. Therefore, it is imperative to evaluate the microbial and inflammatory status of the amniotic fluid to select the subset of women with preterm labor and intact membranes who will benefit from antibiotic treatment. Indeed, recent investigations have demonstrated that the utilization of an appropriate antibiotic regimen can improve adverse perinatal outcomes in women with preterm labor and intact membranes (Yoon et al., 2019), PPROM (Lee et al., 2016a, Lee et al., 2016b), or cervical insufficiency (Oh et al., 2019b, Yeo et al., 2021) who were diagnosed with intra-amniotic infection/inflammation. This antibiotic regimen includes clarithromycin, ceftriaxone and metronidazole, based on their pharmacokinetics (Kafetzis et al., 1983, Visser and Hundt, 1984, Amon, 1985, Matsuda et al., 1988, Witt et al., 2003, Park et al., 2012) and broad coverage for bacteria that are typically found in the amniotic fluid (Romero et al., 1989c, Yoon et al., 1998, DiGiulio et al., 2010, Mendz et al., 2013, Romero et al., 2014b, Romero et al., 2014c, Romero et al., 2015b, Romero et al., 2015d, Romero et al., 2015c). Specifically, the use of clarithromycin is strongly supported by its coverage of genital mycoplasmas as well as more efficient trans-placental passage than other macrolides (Witt et al., 2003, Park et al., 2012). Such protective effects of clarithromycin were recently demonstrated by the reduced rates of preterm birth and neonatal mortality observed in mice treated with this antibiotic after the intra-amniotic injection of *Ureaplasma parvum* (Motomura et al., 2020b). Furthermore, ceftriaxone and metronidazole offer excellent antimicrobial coverage for aerobic and anaerobic bacteria,

respectively (Klein and Cunha, 1995, Freeman et al., 1997, Lamb et al., 2002, Brook et al., 2013), and can also cross the placenta efficiently (Kafetzis et al., 1983, Visser and Hundt, 1984, Amon, 1985, Matsuda et al., 1988). Therefore, this recent evidence supports the use of amniocentesis to evaluate the infectious status of the amniotic fluid and the treatment of intra-amniotic infection with the optimal antibiotic therapy.

Sterile intra-amniotic inflammation: the new kid on the block among the etiologies of preterm labor and birth

Discovery of sterile intra-amniotic inflammation

As mentioned above, the presence of intra-amniotic inflammation has been traditionally attributed to the host defense processes triggered by microbes invading the amniotic cavity (Romero et al., 1987, Romero et al., 1988c, Romero et al., 1989c, Gibbs et al., 1992). However, several clinical investigations have reported that a subset of women diagnosed with intra-amniotic inflammation (as indicated by elevated amniotic fluid IL-6 concentrations (Yoon et al., 2001)) had negative amniotic fluid cultures (Hitti et al., 1997, Yoon et al., 2000a, Yoon et al., 2001, Gardella et al., 2004, DiGiulio et al., 2008, DiGiulio et al., 2010, Combs et al., 2014). Two potential explanations for this phenomenon can be proposed: 1) this subset of women had intra-amniotic inflammation that was initiated by non-cultivable or fastidious microorganisms, or 2) such inflammation was driven by non-infectious processes, as observed in gout, rheumatoid arthritis, or other sterile inflammatory diseases (Busso and So, 2010, Goh and Midwood, 2012, So and Martinon, 2017). Over the past two decades, the advancement of molecular microbiological techniques has allowed for the detection and identification of non-cultivable microbes in the amniotic fluid (Jalava et al., 1996, Oyarzun et al., 1998, Kim et al., 2003, Gardella et al., 2004, DiGiulio et al., 2008, Romero et al., 2014b, Combs et al., 2014, Burnham et al., 2020, Theis et al., 2020, Stinson et al., 2020). Accordingly, our group has utilized a combination of conventional culture and molecular microbiological techniques [PCR-electrospray ionization mass spectrometry (PCR-ESI/MS)](Romero et al., 2014b) as well as microbial cell-free DNA (cfDNA) (Burnham et al., 2020) to demonstrate the absence of bacterial or viral nucleic acids in a subset of women with intra-amniotic inflammation, a condition that has been consequently termed “sterile intra-amniotic inflammation” (Romero et al., 2014c, Romero et al., 2015b, Romero et al., 2015c, Romero et al., 2015a, Burnham et al., 2020) (Fig. 1B). Upon the establishment of this new clinical entity, a new line of investigation has been undertaken by our group and others to evaluate the prevalence and underlying mechanisms of sterile intra-amniotic inflammation. Importantly, sterile intra-amniotic inflammation is more common than intra-amniotic infection in women with preterm labor with intact membranes (Romero et al., 2014c) as well as in women with an asymptomatic sonographic short cervix (Romero et al., 2015c) or cervical insufficiency (Chalupska et al., 2021). Moreover, women with sterile intra-amniotic inflammation have pregnancy and neonatal outcomes similar to women with intra-amniotic infection (Romero et al., 2014c, Combs et al., 2014). The clinical outcomes of sterile intra-amniotic inflammation correlate with the presence of acute inflammatory lesions in the placenta (i.e., acute histologic chorioamnionitis and funisitis), again resembling the outcomes of microbial-associated intra-amniotic inflammation (Romero et al., 2014c). Thus, sterile intra-amniotic

inflammation has emerged as a new entity with pregnancy and neonatal consequences as devastating as those associated with infection, and therefore warrants deeper investigation.

Progress in the understanding of sterile intra-amniotic inflammation

As an initial effort to distinguish the inflammatory processes taking place in sterile intra-amniotic inflammation from those observed in intra-amniotic infection, our group performed a network analysis of the cytokines and other known inflammatory mediators in the amniotic fluid of women who underwent preterm labor with intact membranes and were diagnosed with either sterile intra-amniotic inflammation or intra-amniotic infection (Romero et al., 2015a). This network analysis revealed the enrichment of IL-1α and high mobility group box 1 (HMGB1) in the amniotic fluid of women with sterile intra-amniotic inflammation (Romero et al., 2015a). Multiple studies have demonstrated the importance of IL-1α in the physiologic and pathologic processes of parturition (Romero et al., 1989a, Romero et al., 1990a, Nadeau-Vallee et al., 2016a, Nadeau-Vallee et al., 2016b, Nadeau-Vallee et al., 2017b, Equils et al., 2020), as evidenced by its increased concentrations in the amniotic fluid of women with intra-amniotic inflammation (Romero et al., 1992b) as well as mechanistic demonstrations that the systemic administration of IL-1 induced preterm parturition in mice (Romero et al., 1991a), which could be prevented by pre-treatment with the IL-1 receptor antagonist (IL-1RA) (Romero and Tartakovsky, 1992). Clinical investigations have also shown that women with sterile intra-amniotic inflammation who had higher amniotic fluid concentrations of HMGB1 delivered sooner than women with lower concentrations, implicating this mediator in the pathological process of preterm labor and birth (Romero et al., 2014c). Notably, both IL-1α and HMGB1 are known damage-associated molecular patterns (DAMPs) or alarmins (Oppenheim and Yang, 2005, Lotze et al., 2007, Bianchi, 2007, Rider et al., 2017), and thus our network analysis hinted at a key role for alarmins in the pathophysiology of sterile intra-amniotic inflammation.

Alarmins are considered part of a broad class of molecules, termed danger signals, that alert the innate and adaptive immune system and thus trigger host defense mechanisms (Oppenheim and Yang, 2005, Lotze et al., 2007, Bianchi, 2007, Rider et al., 2017). Danger signals that are derived from exogenous sources, such as microbes, are called pathogen-associated molecular patterns (PAMPs) (Oppenheim and Yang, 2005, Lotze et al., 2007, Bianchi, 2007, Rider et al., 2017). Yet, it is now well known that immune activation can also be induced by endogenous DAMPs or alarmins (Oppenheim and Yang, 2005, Lotze et al., 2007, Bianchi, 2007, Rider et al., 2017). Multiple defining characteristics have been described for alarmins: 1) they are rapidly released upon non-programmed cell death (i.e., necrosis) but not apoptosis; 2) viable cells can also release alarmins via specialized secretion systems or by the endoplasmic reticulum-Golgi secretion pathway; 3) as danger signals, alarmins can participate in the recruitment and activation of innate immune cells via pattern recognition receptors (PRR); and 4) alarmins contribute to the restoration of homeostasis by promoting healing of tissues damaged by inflammation (Oppenheim and Yang, 2005, Lotze et al., 2007, Bianchi, 2007, Rider et al., 2017). In addition, studies have shown that alarmins can be released upon cellular senescence (Huang et al., 2015), a state of cellular aging in which cell division has been halted (Campisi and d'Adda di Fagagna, 2007, Munoz-Espin and Serrano, 2014, Di Micco et al., 2021). Classical alarmins include HMGB1

(Wang et al., 1999, Harris and Raucci, 2006), S100 proteins (Foell et al., 2007), IL-1α (Werman et al., 2004, Tracy et al., 2012, Di Paolo and Shayakhmetov, 2016), and heat-shock protein 70 (HSP70) (Asea et al., 2000), among others (Bianchi, 2007). Importantly, each of the abovementioned alarmins has been demonstrated to be increased in amniotic fluid of women with intra-amniotic inflammation who underwent preterm labor and birth (Romero et al., 1992b, Friel et al., 2007, Romero et al., 2011, Romero et al., 2012, Romero et al., 2014c, Baumbusch et al., 2016, Son et al., 2019, Chaiworapongsa et al., 2008). Based on these observations, we have undertaken a series of translational investigations to establish a causal link between elevated amniotic fluid concentrations of alarmins and preterm birth. The ultrasound-guided intra-amniotic administration of HMGB1 or S100B, at pathological concentrations found in women with sterile intra-amniotic inflammation, induced preterm birth in mice (Gomez-Lopez et al., 2016c, Gomez-Lopez et al., 2019c, Galaz et al., 2021). Similarly, the intra-amniotic injection of the alarmins IL-1α, HSP70, or S100A12 also reduced gestational length, thereby increasing the rate of preterm birth (Motomura et al., 2020a, Schwenkel et al., 2021, Motomura et al., 2021b). Importantly, the intra-amniotic injection of alarmins also induced adverse fetal and neonatal outcomes, as evidenced by a fetal inflammatory response (Kallapur et al., 2011) and increased mortality at birth (Gomez-Lopez et al., 2019c, Motomura et al., 2020a, Motomura et al., 2021b, Schwenkel et al., 2021) as well as postnatal changes such as alterations in respiratory parameters (Emerson et al., 1997, Willet et al., 2002), systemic cortisol levels, and concentration of lung surfactant proteins (Emerson et al., 1997) in neonates. Hence, we have provided solid evidence demonstrating a causal link between the elevated amniotic fluid concentrations of alarmins and preterm birth and adverse neonatal outcomes.

In search of the putative mechanisms whereby alarmins in the amniotic cavity can induce preterm labor and birth, we first turned to the human chorioamniotic membranes. The chorioamniotic membranes are the tissues surrounding the amniotic cavity containing the fetus (Bourne, 1962), and their activation is a component of the common pathway of labor (Norwitz et al., 1999, Romero et al., 2006b, Smith, 2007, Romero et al., 2014c). Given that the chorioamniotic membranes are in direct contact with the amniotic fluid, *in vitro* studies were undertaken to evaluate the pathways that were affected upon exposure of these tissues to HMGB1 (Bredeson et al., 2014, Plazyo et al., 2016, Menon et al., 2016). We showed that HMGB1 induced a pro-inflammatory response in the chorioamniotic membranes by increasing the secretion of IL-6 and mature IL-1β as well as by upregulating the expression of pro-inflammatory transcripts such as *NFKB1*, *ILIB*, *IL6*, *TNF*, *IL1A*, and *IFNG* and the HMGB1 receptors *RAGE* and *TLR2* (Plazyo et al., 2016). Notably, HMGB1 exposure also upregulated the mRNA and protein expression of the inflammasome components nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family pyrin domain-containing 3 protein (NLRP3), NOD 1 and 2, and absent in melanoma 2 (AIM2) in the chorioamniotic membranes (Plazyo et al., 2016). Similarly, we have demonstrated the release of IL-6 and IL-8, the upregulated mRNA expression of *NFKB1*, *ILIB*, *IL6, RAGE*, *TLR2, NOD,* and the increased protein expression of NLRP3 in the chorioamniotic membranes exposed to S100A12 (Motomura et al., 2021b). Taken together, our results demonstrate that alarmins act by inducing inflammatory responses in the human chorioamniotic membranes, a process that involves the NLRP3 inflammasome.

Inflammasomes are cytoplasmic high-molecular-weight protein complexes that coordinate inflammatory responses (Martinon et al., 2002, Mariathasan and Monack, 2007, van de Veerdonk et al., 2011, Gross et al., 2011, Henao-Mejia et al., 2012, Franchi and Nunez, 2012, Swanson et al., 2019). The basic structure of an NLR inflammasome consists of an inflammasome sensor molecule, the adaptor protein ASC (an apoptosis-associated speck-like protein), and pro-caspase-1 (Martinon et al., 2002, Mariathasan and Monack, 2007, van de Veerdonk et al., 2011, Gross et al., 2011, Henao-Mejia et al., 2012, Franchi and Nunez, 2012, Swanson et al., 2019). Upon activation, the inflammasome complex induces the autocatalytic cleavage of pro-caspase-1 into its active form, which can cleave pro-IL-1β and pro-IL-18 into their mature and released forms (Black et al., 1989, Kostura et al., 1989, Cerretti et al., 1992, Thornberry et al., 1992, Gu et al., 1997, Ghayur et al., 1997). These cytokines, which play a key role in term and preterm parturition (Romero et al., 1989a, Romero et al., 1990a, Romero et al., 1991a, Romero et al., 1992b, Romero and Tartakovsky, 1992, Pacora et al., 2000b, Girard et al., 2014), and other components of the NLRP3 inflammasome are increased in amniotic fluid of women who underwent spontaneous term or preterm labor, and such an increase is more pronounced in the presence of intra-amniotic inflammation (Romero et al., 1992b, Pacora et al., 2000b, Gotsch et al., 2008). Furthermore, NLRP3 inflammasome components are also expressed by the chorioamniotic membranes of women with spontaneous term or preterm parturition (Gotsch et al., 2008, Lappas, 2014, Gomez-Lopez et al., 2017e, Gomez-Lopez et al., 2017i, Gomez-Lopez et al., 2017h, Bryant et al., 2017, Romero et al., 2018, Gomez-Lopez et al., 2018b, Gomez-Lopez et al., 2019a, Motomura et al., 2021a), indicating a role for the NLRP3 inflammasome in the inflammatory physiologic or pathologic process of labor. In line with these findings, human and animal studies have shown the increased expression of caspase-1 and mature IL-1β in the chorioamniotic membranes exposed to HMGB1 (Plazyo et al., 2016), IL-1α (Motomura et al., 2020a), S100B (Gomez-Lopez et al., 2019c), and S100A12 (Motomura et al., 2021b). It is also worth mentioning that there is evidence of a causal relationship between the intra-amniotic (Baggia et al., 1996, Sadowsky et al., 2000, Sadowsky et al., 2006, Presicce et al., 2015) or intra-uterine (Yoshimura and Hirsch, 2005) administration of IL-1β and preterm labor in animals.

Once the inflammasome is activated, the ASC adaptor protein assembles into a large intracellular complex known as a “speck” (Fernandes-Alnemri et al., 2007, Vajjhala et al., 2012). Such ASC specks can function as alarmins upon their release into the extracellular space (Balci-Peynircioglu et al., 2008, Baroja-Mazo et al., 2014, Franklin et al., 2014), and thus their detection can serve as an indicator of *in vivo* inflammasome activation (Stutz et al., 2013). Notably, ASC concentrations were increased in amniotic fluid of women with labor at term (Panaitescu et al., 2019), and were higher in women with clinical chorioamnionitis at term and either sterile or microbial-associated intra-amniotic inflammation (Gomez-Lopez et al., 2019e). Importantly, amniotic fluid ASC concentrations were also increased in patients undergoing preterm labor with either sterile intra-amniotic inflammation or intra-amniotic infection (Gomez-Lopez et al., 2018b), providing additional confirmation that both alarmins and microbes can induce inflammasome activation in the amniotic cavity.

The final step of inflammasome activation is pyroptosis, a type of programmed cell death characterized by the release of cytosolic contents through pores formed in the cell membrane by gasdermin D (GSDMD) (Gaidt and Hornung, 2016, Sborgi et al., 2016, Aglietti and Dueber, 2017, Shi et al., 2017), a protein that is cleaved by active caspase-1 and caspase-11 (Kayagaki et al., 2015, Shi et al., 2015). Amniotic fluid concentrations of GSDMD have been utilized as a readout of *in vivo* pyroptosis in the amniotic cavity of women who underwent spontaneous term labor and those with spontaneous preterm labor with intact membranes (Gomez-Lopez et al., 2019f, Gomez-Lopez et al., 2021b). Specifically, GSDMD was detectable in the amniotic fluid and chorioamniotic membranes of women with preterm labor and sterile intra-amniotic inflammation or intra-amniotic infection; moreover, the presence of GSDMD was associated with elevated protein expression of caspase-1 and IL-1β in the chorioamniotic membranes (Gomez-Lopez et al., 2019f). These results provide evidence that women with sterile intra-amniotic inflammation undergo inflammasome-mediated pyroptosis in the intra-amniotic space.

A central question that arose from the abovementioned studies is: what is the origin of the alarmins in the amniotic cavity? Alarmins can be released during cellular senescence (Huang et al., 2015) and as a result of tissue injury or non-programmed cellular death (Oppenheim and Yang, 2005, Lotze et al., 2007, Bianchi, 2007, Rider et al., 2017). Notably, cellular senescence of the chorioamniotic membranes has been considered a physiological mechanism of parturition at term (Behnia et al., 2015, Polettini et al., 2015, Bonney et al., 2016, Velarde and Menon, 2016), and in particular, decidual senescence has been proposed as an independent mechanism involved in non-infection-related spontaneous preterm labor (Hirota et al., 2010, Hirota et al., 2011, Romero et al., 2014a, Deng et al., 2016, Cha and Aronoff, 2017). Hence, we evaluated whether the chorioamniotic membranes from women undergoing preterm labor without acute histologic chorioamnionitis exhibit cellular senescence (Gomez-Lopez et al., 2017d). Such tissues presented signs of cellular senescence (Gomez-Lopez et al., 2017d), and thus represent a potential source of alarmins in the amniotic cavity of women with sterile intra-amniotic inflammation who underwent preterm labor and birth.

The studies described herein provide evidence for a role of alarmins and the NLRP3 inflammasome in the chorioamniotic membranes in sterile intra-amniotic inflammation. However, whether the intra-amniotic inflammatory response driven by alarmins is distinct from that initiated by invading microbes is a subject of ongoing investigation. We sought to characterize the transcriptomic differences between the chorioamniotic membranes from women who underwent spontaneous preterm labor with intact membranes and sterile intra-amniotic inflammation and those with intra-amniotic infection by utilizing RNA sequencing (Motomura et al., 2021a). Significant transcriptomic differences were found in the chorioamniotic membranes from women with sterile intra-amniotic inflammation compared to the other study groups, and the immune response in this tissue was milder than that induced by microbes. Importantly, such a response included the upregulation of transcripts for the alarmin *S100A8* as well as the inflammasome-related molecules *PYCARD*, *AIM2*, and *NLRC4* (Motomura et al., 2021a). Furthermore, the chorioamniotic membrane transcriptomes from women with intra-amniotic infection clustered separately from those of women with sterile intra-amniotic inflammation or without inflammation, thus

further confirming the distinct nature of the immune response taking place during sterile intra-amniotic inflammation (Motomura et al., 2021a).

Collectively, the abovementioned investigations implicate sterile intra-amniotic inflammation as a new clinical entity that can lead to adverse perinatal outcomes. Such a distinct inflammatory response is triggered by alarmins and involves the activation of the NLRP3 inflammasome in the amniotic cavity.

Can we treat sterile intra-amniotic inflammation to prevent preterm birth?

In general, the treatment of sterile inflammatory processes includes the use of anti-inflammatory medications such as non-steroidal anti-inflammatory (Fullerton, 2013) or corticosteroid (Dougherty and Schneebeli, 1955, Coutinho and Chapman, 2011, Busillo and Cidlowski, 2013) drugs. Other treatments that specifically decrease the concentration of alarmins driving sterile inflammation have also been utilized to treat gout (Terkeltaub, 2003, Pacher et al., 2006, Khanna et al., 2012). However, the majority of these drugs utilized to treat sterile inflammation-related pathologies are not approved for use during pregnancy. Therefore, to date there is no approved treatment for sterile intra-amniotic inflammation. Given the abovementioned role of the NLRP3 inflammasome in sterile intra-amniotic inflammation, we have proposed that the inhibition of NLRP3 inflammasome activation could be used to improve perinatal outcomes. MCC950 is a specific inhibitor of the NLRP3 inflammasome that has been utilized in multiple animal models of diseases such as colitis (Perera et al., 2018), traumatic brain injury (Ismael et al., 2018a, Xu et al., 2018a), and stroke (Ismael et al., 2018b), among others (van der Heijden et al., 2017, Zhai et al., 2018). Therefore, we induced sterile intra-amniotic inflammation in mice via the ultrasound-guided intra-amniotic injection of S100B and showed that treatment with MCC950 drastically reduced preterm birth and neonatal mortality (Gomez-Lopez et al., 2019c). As further proof of this mechanism, we induced sterile intra-amniotic inflammation in *Nlrp3*$^{-/-}$ mice using IL-1α or S100B and showed that preterm birth and neonatal mortality were similarly reduced ((Motomura et al., 2020a) and Gomez-Lopez et al., unpublished data). However, MCC950 is not approved for use during pregnancy and requires additional research to assess its safety in this regard. Given that IL-1β is a product of inflammasome activation, animal models of intra-amniotic or intra-uterine injection of IL-1β have been utilized to test treatments for intra-amniotic inflammation-associated preterm birth (Sadowsky et al., 2000, Sadowsky et al., 2003, Yoshimura and Hirsch, 2005). Pre-treatment with indomethacin, a tocolytic agent that can be used to delay preterm labor, reduced uterine contractions in catheterized macaques intra-amniotically injected with IL-1β (Sadowsky et al., 2000). Yet, in humans, indomethacin is only recommended for use until 32 weeks of gestation, given the increased risk of closure of the ductus arteriosus in fetuses exposed to it, which limits its potential utility for preventing preterm birth (Vermillion et al., 1997, Macones et al., 2001, American College of Obstetricians and Gynecologists, 2016). Similarly, pre-treatment with either dexamethasone or IL-10 reduced the uterine contractility and the intra-amniotic inflammation induced by the intra-amniotic administration of IL-1β in macaques (Sadowsky et al., 2003). Moreover, pre-treatment with a non-competitive IL-1 receptor ligand, Rytvela, prevented intra-uterine IL-1β-induced preterm birth in mice (Nadeau-Vallee et al., 2017a). Yet, further studies are required to address the safety and usefulness of this promising tool

during human pregnancy. Furthermore, to date there are no predictive tools for determining women at risk of sterile intra-amniotic inflammation, and thus pre-treatments are difficult to translate into a clinical setting. Therefore, we explored approaches currently approved for use during pregnancy that could be used to treat sterile intra-amniotic inflammation.

The drug development process can take several years from the discovery to their approval (Kaitin, 2010, Hughes et al., 2011). This process is even more complex during pregnancy due to the physiological changes of pregnant women and the imminent risk of fetal damage (Sheffield et al., 2014, Chappell and David, 2016, Ren et al., 2021). Therefore, the repurposing of drugs that are already approved to be utilized during pregnancy is an optimal approach. Under this premise, and given the urgency to find a treatment for sterile intra-amniotic inflammation, we have investigated two medications that are widely utilized during pregnancy: betamethasone (Galaz et al., 2021) and clarithromycin (Galaz et al., submitted). Betamethasone is a corticosteroid that has become the standard of care for women at risk of delivering preterm, as it has been shown to accelerate fetal organ maturation (American College of Obstetricians and Gynecologists, 2017, McGoldrick et al., 2020). As a corticosteroid, betamethasone has been demonstrated to reduce inflammatory processes in multiple clinical settings (Corbett et al., 1993, Corbel et al., 1999, Matsuo et al., 2009, Ly and Amici, 2018, Zhao et al., 2021). Thus, we recently utilized our model of HMGB1-induced sterile intra-amniotic inflammation to demonstrate that treatment with betamethasone prevented preterm birth; yet, it did not reduce neonatal mortality (Galaz et al., 2021). Ongoing research is investigating the mechanisms whereby betamethasone can extend gestational length. On the other hand, clarithromycin is a macrolide that, together with other antibiotics, has emerged as an effective treatment to be used in the context of intra-amniotic infection/inflammation in women with preterm labor with intact membranes (Yoon et al., 2019), PPROM (Lee et al., 2016a, Lee et al., 2016b), and cervical insufficiency (Oh et al., 2019b, Yeo et al., 2021). Clarithromycin exhibits potent anti-inflammatory properties by acting through the NF-κB and AP-1 pathways (Kikuchi et al., 2002, Yamamoto et al., 2017). Moreover, clarithromycin is the macrolide that most efficiently crosses the placenta (Witt et al., 2003). Importantly, a recent study showed that clarithromycin reduced the amniotic fluid concentrations of IL-6 in women with PPROM and sterile intra-amniotic inflammation (Kacerovsky et al., 2020). Therefore, we undertook a series of animal experiments to investigate whether clarithromycin can be utilized to prevent preterm birth and adverse neonatal outcomes in a model of alarmin-induced sterile intra-amniotic inflammation as well as the underlying mechanisms of action (Galaz et al., submitted). We demonstrated that treatment with clarithromycin prevented HMGB1-induced preterm birth by interfering with the common pathway of parturition as evidenced by dysregulated expression of contractility-associated proteins and inflammatory mediators in the intra-uterine tissues. Notably, clarithromycin improved neonatal mortality by dampening inflammation in the placenta as well as in the fetal lung, intestine, liver, and spleen (Galaz et al., submitted). However, HMGB1-induced neonatal mortality was not fully rescued by clarithromycin treatment. It is worth mentioning that women at risk of preterm birth due to intra-amniotic inflammation/infection are treated with both corticosteroids and antibiotics simultaneously (Lee et al., 2016b, Oh et al., 2019b, Yoon et al., 2019, American College of Obstetricians and Gynecologists, 2020). Hence, further research is required to address

whether the combination of betamethasone and clarithromycin, or different drugs that could have synergistic effects, can be used to treat the adverse pregnancy and neonatal outcomes caused by sterile intra-amniotic inflammation.

A unique type of intra-amniotic inflammation driven by fetal T-cell activation: a novel mechanism for preterm labor and birth

The clinical definition of intra-amniotic inflammation considers only the elevated amniotic concentrations of established biomarkers such as IL-6 or MMP-8 (Park et al., 2001, Yoon et al., 2001). Yet, inflammation as a general concept comprises systemic or tissue-wide reaction involving a diverse array of cellular and soluble immune mediators at sites of infection or injury (Abbas et al., 2016). In line with this concept, it has been demonstrated that the intra-amniotic inflammatory response involves the active participation of both maternal and fetal immune cells. Indeed, a pioneer study showed that fetal innate immune cells in the human umbilical cord blood are activated in cases of preterm labor leading to preterm birth compared to term deliveries (Berry et al., 1995). Notably, in this study the cord blood was obtained prior to birth (via cordocentesis), and only a fraction of the preterm neonates were exposed to microbes, thereby suggesting that the fetus itself is able to respond or cause the process of labor (Berry et al., 1995). More recently, we showed that the cord blood of preterm neonates has a population of central memory Th1 cells that is absent in term neonates (Frascoli et al., 2018). Such T cells specifically responded to maternal alloantigens and induced myometrial contractility *in vitro* (Frascoli et al., 2018). Last, the adoptive transfer of activated T cells into the fetal mice induced pregnancy loss, providing *in vivo* evidence of a role for activated T cells in adverse pregnancy outcomes (Frascoli et al., 2018). Hence, these studies provided insight into the functions of the fetal adaptive immune system and suggested that the fetus could trigger preterm labor. To confirm these findings, we utilized amniotic fluid samples, which allow the study of the *in utero* fetal immune response (Gomez-Lopez et al., 2018c). Specifically, we have previously demonstrated the presence of multiple immune cell populations in the amniotic fluid that vary throughout gestation in the absence of intra-amniotic inflammation (Gomez-Lopez et al., 2018c). A prior study also noted that fetal innate lymphoid cells (ILCs) are present in amniotic fluid of women in the absence of intra-amniotic inflammation/infection and that such cells expressed a phenotype indicative of intra-epithelial localization (Marquardt et al., 2016), suggesting that they are derived from fetal tissues and can respond to intra-amniotic inflammation. In light of the above evidence, we evaluated amniotic fluid samples and showed that T cells represent a major subset of leukocytes in preterm pregnancies and that such cells were of fetal origin, as indicated by DNA fingerprinting (Gomez-Lopez et al., 2019g). We also found that fetal CD4+ T cells, but none of the other evaluated leukocyte subsets, were increased in amniotic fluid of women with idiopathic preterm labor (i.e., without intra-amniotic inflammation/infection), which represents the largest subset of preterm labor cases (Gomez-Lopez et al., 2019g). Consistent with the abovementioned findings in amniotic fluid ILCs (Marquardt et al., 2016), fetal T cells expressed markers indicative of mucosal residence, confirming that these cells did not originate from the fetal circulation (Gomez-Lopez et al., 2019g). Furthermore, fetal CD4+ T cells from amniotic fluid samples express cytokines typical of T-cell activation (IL-2, IL-4, and IL-13), suggesting a mild and distinct immune

response in idiopathic preterm labor. Moreover, *in vitro* experiments showed that umbilical cord blood T cells from neonates born to mothers who underwent idiopathic preterm labor and birth displayed enhanced responsiveness compared to those from neonates delivered at term (Gomez-Lopez et al., 2019g), providing novel evidence that fetal T-cell activation is associated with idiopathic preterm labor and birth (Gomez-Lopez et al., 2019g). Last, the ultrasound-guided intra-amniotic injection of activated neonatal CD4+ T cells in pregnant mice resulted in preterm delivery, demonstrating that activated fetal T cells are capable of triggering preterm parturition and, therefore, represent a new mechanism of disease for idiopathic preterm birth (Gomez-Lopez et al., 2019g) (Fig. 1C). Yet, further studies are warranted to understand the mechanisms responsible for the premature activation of fetal T cells in the amniotic cavity.

Maternal immune contributions to the etiology of preterm labor and birth

Effector and regulatory T cells

The earliest hypotheses for the seemingly paradoxical nature of pregnancy were prompted by advances in the understanding of immunological tolerance, most notably those pioneered by Peter Medawar (Medawar, 1953, Billington, 2003), the father of reproductive immunology. In one of the most widely recognized works in the field of reproduction, Medawar postulated several reasons why the maternal immune system did not reject the fetus: 1) complete anatomic separation of the mother and fetus; 2) lack of antigenic potential by the fetus; or 3) inertness or unresponsiveness of the maternal immune system (Medawar, 1953). While later investigations have disqualified the first two hypotheses, the third has since been shown to have merit. Rather than complete inertness, it is now clear that pregnancy represents a state of immunological tolerance during which the mother must tolerate the semi-allograft fetus (Chaouat et al., 1979, Bonney and Onyekwuluje, 2003, Zenclussen et al., 2005, Robertson et al., 2009, Kahn and Baltimore, 2010, Shima et al., 2010, Zenclussen et al., 2010, Dimova et al., 2011, Rowe et al., 2012, Samstein et al., 2012, Ramhorst et al., 2012, Shima et al., 2015), with a growing body of evidence suggesting that the fetus also tolerates the mother (Mold et al., 2008, Ivarsson et al., 2013, McGovern et al., 2017, Frascoli et al., 2018). The maternal immune system is constantly exposed to foreign paternal/fetal antigens (Herzenberg et al., 1979, Bianchi et al., 1996, Knight et al., 1998, Germain et al., 2007, Holland et al., 2012, Stenqvist et al., 2013, Gohner et al., 2017, Tong et al., 2018, Arenas-Hernandez et al., 2021), resulting in a series of local (Erlebacher et al., 2007, Bizargity et al., 2009, Samstein et al., 2012, Shima et al., 2015) and systemic (Chaouat et al., 1979, Bonney and Onyekwuluje, 2003, Aluvihare et al., 2004, Zenclussen et al., 2005, Bizargity et al., 2009, Shima et al., 2010, Kahn and Baltimore, 2010, Rowe et al., 2012, Samstein et al., 2012) immunological adaptations that are collectively termed “maternal-fetal tolerance.” Among the mediators that foster and sustain maternal-fetal tolerance, adaptive immune cells such as effector T cells (Vargas et al., 1993, Tilburgs et al., 2006, Taglauer et al., 2008, Wang et al., 2015, Powell et al., 2017, Terzieva et al., 2019, Arenas-Hernandez et al., 2019) and regulatory T cells (Tregs) (Aluvihare et al., 2004, Sasaki et al., 2004, Heikkinen et al., 2004, Sindram-Trujillo et al., 2004, Wang et al., 2015, Tsuda et al., 2018, Salvany-Celades et al., 2019, Gomez-Lopez et al., 2020) perform critical functions. Both cell types participate in mediating the complex immunological scenario of

pregnancy in which maternal-fetal tolerance must occur (Bonney and Onyekwuluje, 2003, Aluvihare et al., 2004, Zenclussen et al., 2005, Kahn and Baltimore, 2010, Shima et al., 2010, Samstein et al., 2012, Rowe et al., 2012, Svensson-Arvelund et al., 2015, Shima et al., 2015) but also remain vigilant against external threats (e.g., infection) (Bizargity et al., 2009, Arenas-Hernandez et al., 2016, van Egmond et al., 2016, van der Zwan et al., 2018). Therefore, disruptions or alterations in the activity of these different immune cell subsets is often associated with adverse pregnancy outcomes (Sasaki et al., 2004, Zenclussen et al., 2005, Shima et al., 2010, Jianjun et al., 2010, Yamada et al., 2012, Care et al., 2018, Tsuda et al., 2018, Arenas-Hernandez et al., 2019, Tsuda et al., 2021).

Effector T cells—After encountering their specific antigen, circulating naïve T cells proliferate and differentiate to perform effector functions and eliminate threats (Bachmann et al., 1999). Such T cells are subsequently termed “memory” T cells and can be subdivided into central, effector, and terminally differentiated effector memory T cells based on their functional state and localization to secondary lymphoid organs or the circulation (Sallusto et al., 1999, Geginat et al., 2003, D’Asaro et al., 2006). Moreover, CD4+ and CD8+ T cells can differentiate into one of several effector subsets including T helper type 1 (Th1)/T cytotoxic type 1 (Tc1), Th2/Tc2, Th9/Tc9, and Th17/Tc17 cells according to stimuli provided by the surrounding microenvironment (Brummelman et al., 2018, Saravia et al., 2019). Due to the tightly controlled immunological balance at the maternal-fetal interface, effector T cells were conventionally thought to be absent from this compartment. Indeed, the combination of tissue-specific anti-T-cell mechanisms (Daya et al., 1987, Nancy et al., 2012) together with the presence of Tregs (Aluvihare et al., 2004, Heikkinen et al., 2004, Sasaki et al., 2004, Svensson-Arvelund et al., 2015, Tsuda et al., 2018, Salvany-Celades et al., 2019, Gomez-Lopez et al., 2020) and other homeostatic immune cells such as macrophages (Hunt et al., 1984, Gustafsson et al., 2008, Houser et al., 2011, Svensson et al., 2011, Svensson-Arvelund et al., 2015, Xu et al., 2016, Gomez-Lopez et al., 2021a) makes the decidua a largely unwelcoming site for effector T cells, and as a consequence some of the T cells residing in this compartment display exhausted or senescent phenotypes (Wang et al., 2015, van der Zwan et al., 2018, Slutsky et al., 2019). However, as the end of pregnancy approaches, both human (Gomez-Lopez et al., 2009, Gomez-Lopez et al., 2011, Gomez-Lopez et al., 2013) and animal (Heyborne et al., 1992, Furcron et al., 2015, Arenas-Hernandez et al., 2016, St Louis et al., 2016, Gomez-Lopez et al., 2017a, Arenas-Hernandez et al., 2019, Gomez-Lopez et al., 2020, Stas et al., 2020) studies have demonstrated that T cells migrate to the maternal-fetal interface, where they acquire distinct activated phenotypes (Sindram-Trujillo et al., 2003, Tilburgs et al., 2009a, Tilburgs et al., 2009b, Tilburgs et al., 2010, Arenas-Hernandez et al., 2019). Indeed, decidual T cells show increased expression of activation markers such as CD25, CD38, or CD69 (Abadia-Molina et al., 1996, Sindram-Trujillo et al., 2004, Arenas-Hernandez et al., 2019) as well as labor-associated inflammatory mediators (Joachim et al., 2001, Gomez-Lopez et al., 2013).

Given their participation in normal parturition at term, effector T cells have also been implicated in the premature onset of labor. The invasion of cytotoxic T cells into the decidual tissues, termed chronic histological chorioamnionitis, is frequently observed in pregnancies with complications such as spontaneous preterm birth (Kim et al., 2015). More

recently, we showed that effector and activated T cells expressing perforin and granzyme B are enriched at the maternal-fetal interface of women who underwent spontaneous preterm labor and birth (Arenas-Hernandez et al., 2019) (Fig. 2A). Consistent with such human findings, the administration of an anti-CD3 antibody to pregnant mice induced the systemic activation of T cells, resulting in preterm birth (Gomez-Lopez et al., 2016b, Arenas-Hernandez et al., 2019) through inflammatory mechanisms that are distinct from those observed in other well-known preterm birth models (Fidel et al., 1994, Dudley et al., 1996, Nadeem et al., 2016, Gomez-Lopez et al., 2018a, Arenas-Hernandez et al., 2019). Furthermore, we recently demonstrated that a subset of decidual T cells co-express IL-22 and RORγt, and that such cells are enriched in women who underwent preterm labor and birth (Gershater et al., 2022, Accepted). The expression of these two molecules, together with the absence of IL-17A, allowed us to propose that such decidual T cells belong to the Th22 subset (Duhen et al., 2009, Liu et al., 2009, Nograles et al., 2009, Trifari et al., 2009). Our finding that Th22-like cells are present at the maternal-fetal interface of women with preterm labor is in line with a previous study showing that decidual IL-22-expressing T cells are implicated in pregnancy loss (Logiodice et al., 2019). Hence, T cells expressing IL-22 are present at the maternal-fetal interface in early and late pregnancy, where they seem to participate in the mechanisms involved in obstetrical disease.

IL-17-producing T cells (Th17 cells) are a subset of conventionally pro-inflammatory effector T cells that participate in host defense at mucosal/barrier surfaces (Stockinger and Omenetti, 2017). Such cells have been reported as residing at the maternal-fetal interface in early pregnancy (Wu et al., 2014, Lombardelli et al., 2016), and a disruption of the balance between Th17 cells and Tregs is implicated in early pregnancy complications (i.e., spontaneous abortion) (Wang et al., 2010, Nakashima et al., 2010, Lee et al., 2011, Lee et al., 2012, Wu et al., 2016, Zhu et al., 2017). In late pregnancy, studies have suggested that Th17 cells also contribute to the pathophysiology of preeclampsia (Santner-Nanan et al., 2009, Saito, 2010, Fu et al., 2014, Zhang et al., 2018). Notably, such cells are more prevalent in the chorioamniotic membranes from cases of preterm birth with acute chorioamnionitis than in cases without, suggesting that Th17 cells are associated with inflammatory processes at the maternal-fetal interface of women with preterm labor and birth (Ito et al., 2010, Fedorka et al., 2021). In addition to Th17 cells, we have proposed that, under specific conditions, IL-22 is expressed by maternal T cells in the uterine decidua of women with preterm labor and birth (Gershater et al., 2022, Accepted). Under pathological circumstances associated with maternal T-cell activation, IL-22 can cross the maternal-fetal interface and reach the amniotic cavity where it is sensed by the fetal and gestational tissues, causing fetal injury that can lead to neonatal death (Gershater et al., 2022, Accepted).

Regulatory T cells—Regulatory T cells play an important role in mediating immune tolerance in a variety of clinical contexts such as autoimmune disease and transplantation. Consequently, it is unsurprising that Tregs are critical drivers of maternal-fetal tolerance (Chaouat et al., 1979, Bonney and Onyekwuluje, 2003, Aluvihare et al., 2004, Sasaki et al., 2004, Heikkinen et al., 2004, Zenclussen et al., 2005, Robertson et al., 2009, Kahn and Baltimore, 2010, Shima et al., 2010, Samstein et al., 2012, Rowe et al., 2012, Jiang et al., 2014, Svensson-Arvelund et al., 2015, Shima et al., 2015, Bonney, 2016, Tsuda et al., 2018,

Salvany-Celades et al., 2019, Gomez-Lopez et al., 2020, Zhang et al., 2021). Conventional Tregs are described as $CD4^+CD25^+Foxp3^+$ cells that display potent immunosuppressive functions (Sakaguchi et al., 1985, Fontenot et al., 2003). The Treg subset includes thymic/natural Tregs and peripheral/induced Tregs (Yuan and Malek, 2012, Abbas et al., 2013): whereas natural Tregs are considered important in the context of autoimmunity (Jordan et al., 2001, Apostolou et al., 2002, Kumar et al., 2019), peripheral Tregs contribute to mucosal immunity (Haribhai et al., 2011, Josefowicz et al., 2012), which includes maternal-fetal tolerance (Sasaki et al., 2004, Zenclussen et al., 2005, Robertson et al., 2009, Guerin et al., 2009, Zenclussen et al., 2010, Samstein et al., 2012, Rowe et al., 2012, Robertson et al., 2018, Schjenken et al., 2020). Tregs exhibit their immunosuppressive functions through several mechanisms, including secretion of TGF-β (Read et al., 2000, Nakamura et al., 2001) and IL-10 (Asseman et al., 1999, Annacker et al., 2001) that exert paracrine actions on surrounding cells. While a number of studies have established the importance of Tregs during pregnancy establishment and maintenance (Zenclussen et al., 2005, Darrasse-Jèze et al., 2006, Kahn and Baltimore, 2010, Shima et al., 2010, Rowe et al., 2011, Samstein et al., 2012, Rowe et al., 2012, Chen et al., 2013, Diao et al., 2021), recent investigations have also pointed to a role for these adaptive immune cells in late pregnancy (Gomez-Lopez et al., 2020), when most obstetrical diseases manifest (Goldenberg et al., 2008). Tregs are present at the maternal-fetal interface throughout the third trimester prior to labor at term (Tilburgs et al., 2006, Tilburgs et al., 2008, Galazka et al., 2009, Salvany-Celades et al., 2019, Gomez-Lopez et al., 2020), where their proportions were altered compared to women who delivered without labor (Sindram-Trujillo et al., 2004, Galazka et al., 2009). Such observations have been confirmed in mice, where a decidual Treg population was reported (Furcron et al., 2015, Furcron et al., 2016, Gomez-Lopez et al., 2016a). Thus, Tregs represent a component of the immune repertoire at the maternal-fetal interface in late pregnancy.

Alterations in systemic or local Tregs (Sasaki et al., 2007, Prins et al., 2009, Quinn et al., 2011, Nguyen et al., 2017, Tsuda et al., 2018) as well as the Th17/Treg balance (Santner-Nanan et al., 2009, Ding et al., 2019) have been implicated in the pathogenesis of preeclampsia, emphasizing the importance of this adaptive immune subset throughout pregnancy. Yet, little was known of a direct contribution of these cells to spontaneous preterm labor and birth. Accordingly, we recently reported that a subset of women with idiopathic preterm labor and birth displayed a reduction in functional Tregs at the maternal-fetal interface (Gomez-Lopez et al., 2020). This finding correlates with clinical reports showing that women who underwent preterm labor and birth have reduced numbers and function of Tregs in the maternal circulation (Xiong et al., 2010, Schober et al., 2012). Consequently, we utilized a murine model of maternal Treg depletion to demonstrate that the systemic deficiency of Tregs can lead to preterm birth in first and repeat pregnancies; moreover, the loss of such cells induces adverse neonatal outcomes (Gomez-Lopez et al., 2020). The mechanisms whereby the loss of Tregs induces adverse perinatal outcomes involved alterations in the cellular and soluble immune responses in the mother and at the maternal-fetal interface as well as dysregulation of developmental and cellular processes in the placenta (Gomez-Lopez et al., 2020). As a secondary effect, the loss of Tregs also increased maternal susceptibility to preterm birth induced by the administration of LPS (Gomez-Lopez et al., 2020). Importantly, the observed adverse perinatal outcomes were

rescued by the adoptive transfer of polyclonal expanded Tregs (Gomez-Lopez et al., 2020). Therefore, we suggested that Tregs play a central role during late pregnancy by modulating systemic and local cellular responses, and that alterations in the proportions or functionality of such cells can promote a pro-inflammatory environment resulting in the development of obstetrical complications such as spontaneous preterm labor in addition to increased susceptibility to infection-induced preterm birth (Fig. 2A).

Potential interventions—The evidence presented above underscores the importance of the balance between Treg immunosuppressive functions throughout pregnancy and the controlled activity of effector T cells for successful maternal-fetal tolerance. Thus, pregnancy interventions that promote such a balance, whether directly or as a secondary effect, are of great interest. We have shown that two commonly utilized treatments, vaginal progesterone and human chorionic gonadotropin (hCG), both display immunomodulatory effects that include an increased proportion of Tregs in the decidual tissues in mice (Furcron et al., 2015, Furcron et al., 2016). Such an effect is likely mediated through the glucocorticoid receptor (GR) by which progesterone can induce conventional T-cell apoptosis, thereby resulting in an increased proportion of Tregs (Engler et al., 2017). We have also shown that progesterone exerts complementary reduction of inflammatory responses at the maternal-fetal interface in a model of systemic maternal T-cell activation-induced preterm birth (Arenas-Hernandez et al., 2019), and thus such a treatment can address both components of effector T cell/Treg imbalance associated with preterm birth.

A number of different cellular and molecular approaches directed at conventional T cells or Tregs have been utilized to treat conditions such as autoimmune disease or graft-versus-host disease (GVHD) (Esensten et al., 2018, Ferreira et al., 2019). While successful in some cases, the potential application of such treatments during pregnancy highlights some challenges. With regard to cellular approaches, multiple clinical trials have shown benefits of administering *ex vivo* expanded polyclonal Tregs to patients with various diseases (Esensten et al., 2018); yet, animal studies have indicated that infusion of antigen-specific Tregs may be more potent in conditions such as diabetes (Green et al., 2002, Tang et al., 2004, Esensten et al., 2018). In one of these studies, it was demonstrated that adoptively transferring Tregs derived from the pancreatic lymph nodes to recipient mice prevented diabetes development (Green et al., 2002); however, such a strategy would be largely non-applicable in humans, particularly during pregnancy, as obtaining Tregs from lymphoid organs adjacent to the target tissue is not feasible. Nonetheless, we have shown that the adoptive transfer of polyclonal Tregs in mice could successfully prevent the impending adverse pregnancy outcomes induced by a reduction of these cells (Gomez-Lopez et al., 2020). For the majority of diseases, the use of engineered T-cell receptors (TCRs) or chimeric antigen receptor (CAR) Tregs can be applied at least in theory, given that candidate antigens have typically been identified (Ferreira et al., 2019). On the other hand, while it is presumed that paternal/fetal antigens are those driving maternal anti-fetal rejection, the identification of epitopes that could be used to engineer specific Tregs is difficult and remains a major limitation of immunological investigations during pregnancy.

Aside from cellular therapies, strategies to take advantage of the mediators required for and produced by effector and regulatory T cells have also been explored for treating

inflammatory diseases. Interleukin-2 is essential for the development and suppressive functions of Tregs, which constitutively express CD25 [a component of the high-affinity IL-2 receptor (Tang, 2015)]. Thus, it was reasoned that low-dose IL-2 treatment could preferentially boost Tregs without initiating systemic immune activation (Tang, 2015). Prior and ongoing clinical trials have shown some success in alleviating symptoms in patients with GVHD or systemic lupus erythematosus (SLE), among others (Ferreira et al., 2019), and it is possible that a combination of expanded Treg infusion together with low-dose IL-2 could ensure that transferred cells are maintained and even expanded. However, normal pregnancy is characterized by low-grade systemic inflammation and immune activation (Sacks et al., 1998, Naccasha et al., 2001, Kraus et al., 2012) that can be exacerbated in the context of disease, and thus substantial research is required to evaluate whether the administration of IL-2 during pregnancy would be detrimental. The corticosteroid prednisone is clinically used in a variety of immune-related diseases and can promote the function and expansion of Tregs (Fu et al., 2019). Indeed, *in vitro* prednisone treatment increased the proportion of Tregs among isolated first trimester decidual lymphocytes and inhibited Th17 cells (Fu et al., 2017). Moreover, a clinical trial provided evidence that prednisone increased peripheral Tregs and improved pregnancy success in repeated implantation failure (RIF) patients (Huang et al., 2021). Last, vitamin D exerts well-documented anti-inflammatory effects that include induction of IL-10 and inhibition of Th9 and Th17 cells (Palmer et al., 2011, Korf et al., 2012). Indeed, given its modulation of the Treg/Th17 ratio, insufficient vitamin D has been implicated in pregnancy complications such as preeclampsia (Muyayalo et al., 2019, Ribeiro et al., 2021), preterm labor (Zahran et al., 2018), and recurrent pregnancy loss (Ji et al., 2019), which could be improved by supplementation (Chen et al., 2020). Thus, a number of treatment options exist that could be utilized to boost Treg functions and numbers and potentially improve pregnancy outcomes.

An alternative approach to boosting Tregs could be the targeted inhibition of specific mediators released by effector T-cell subsets. An ongoing line of investigation in our laboratory has indicated that the cytokine IL-22, which is primarily produced by the Th22 subset (in the absence of IL-17A) at the maternal-fetal interface, can cross from the maternal side to the amniotic cavity and be sensed by the binding protein expressed by fetal and gestational tissues, causing tissue damage and leading to adverse short- and long-term neonatal outcomes (Gershater et al., 2022, Accepted). Thus, in the context of specific pregnancy complications, therapeutic approaches directed at diminishing the concentrations or activity of specific T cell-associated mediators could also represent a viable approach.

Homeostatic and pro-inflammatory macrophages

The evidence provided above demonstrates that Tregs are an essential component of maternal-fetal tolerance. Yet, we have shown using animal models that the impaired presence of Tregs in late pregnancy only accounts for a small proportion of preterm births (Gomez-Lopez et al., 2020). Therefore, we considered that other immune cells besides Tregs must participate in maintaining maternal-fetal homeostasis. Macrophages constitute the second-largest population of leukocytes (20–30%) at the maternal-fetal interface (Lessin et al., 1988, Williams et al., 2009), and contribute to multiple processes required for pregnancy establishment including embryo implantation (Jaiswal et al., 2012, Care et al.,

2013, Schumacher et al., 2018), trophoblast invasion (Tan et al., 2014, Ding et al., 2021), and spiral artery remodeling (Hazan et al., 2010, Lash et al., 2016). In addition, a large number of investigations have explored the phenotypes of decidual macrophages and noted that the majority of this subset display unique functions and phenotypes that most closely resemble anti-inflammatory or M2-like macrophages (Hunt et al., 1984, Gustafsson et al., 2008, Nagamatsu and Schust, 2010, Svensson et al., 2011, Houser et al., 2011, Svensson-Arvelund et al., 2015, Svensson-Arvelund and Ernerudh, 2015, Xu et al., 2016, Chambers et al., 2020). Therefore, we recently proposed that macrophages in the uterine decidua exert anti-inflammatory functions during late pregnancy that promote maternal-fetal homeostasis and thereby sustain gestation prior to term labor (Gomez-Lopez et al., 2021a) (Fig. 2B). We applied a model of pregnant *Cd11b*$^{DTR/DTR}$ mice wherein CD11b+ macrophages could be depleted upon administration of diphtheria toxin (Duffield et al., 2005, Cailhier et al., 2005), which has been shown to impair fetal development (Yellon et al., 2019) and result in pregnancy loss in early gestation (Robertson et al., 2008, Care et al., 2013). Using this approach, we demonstrated that macrophage depletion in late pregnancy resulted in preterm birth in the majority of dams (75%) (Gomez-Lopez et al., 2021a). More importantly, the majority of pups born to macrophage-depleted dams did not survive past the first 24 hours of life, suggesting that the loss of maternal macrophages may have adverse effects beyond intra-uterine life (Gomez-Lopez et al., 2021a). A causal link between maternal macrophage depletion and adverse pregnancy outcomes was mechanistically demonstrated by adoptively transferring bone marrow-derived macrophages (BMDMs) into macrophage-depleted dams, which successfully reduced the preterm birth rate but did not improve neonatal survival (Gomez-Lopez et al., 2021a). We reasoned that, given the homeostatic phenotypes attributed to macrophages at the maternal-fetal interface (Hunt et al., 1984, Gustafsson et al., 2008, Nagamatsu and Schust, 2010, Svensson et al., 2011, Houser et al., 2011, Svensson-Arvelund et al., 2015, Svensson-Arvelund and Ernerudh, 2015, Xu et al., 2016, Chambers et al., 2020), the *in vitro* polarization of BMDMs prior to their adoptive transfer may improve their effectiveness. We utilized our translationally-relevant model of intra-amniotic inflammation induced by the ultrasound-guided intra-amniotic injection of LPS to demonstrate that the administration of M2-polarized macrophages not only drastically reduced preterm births but decreased neonatal mortality, thereby demonstrating the importance of homeostatic macrophages for pregnancy maintenance as well as neonatal survival (Gomez-Lopez et al., 2021a). Molecular investigation revealed that the adoptive transfer of M2-polarized macrophages reduced inflammation in the maternal circulation and amniotic fluid as well as downregulated inflammatory gene expression in fetal tissues such as the brain and lung (Gomez-Lopez et al., 2021a), providing mechanistic insight into the protective effects of these homeostatic cells for the mother and fetus.

Although the majority of macrophages at the maternal-fetal interface display homeostatic or anti-inflammatory phenotypes, the presence of pro-inflammatory macrophages has also been documented in the context of physiological (Repnik et al., 2008, Xu et al., 2016, Chambers et al., 2020) or pathological (Hamilton et al., 2012, Xu et al., 2016) labor. During normal labor at term, an influx of myeloid cells such as macrophages occurs at the maternal-fetal interface (Young et al., 2002, Osman et al., 2003, Shynlova et al., 2013, Xu et al., 2016, Sharps et al., 2020) as well as in the uterine (Thomson et al., 1999, Mackler et al., 1999,

Young et al., 2002, Osman et al., 2003, Gomez-Lopez et al., 2010, Wahid et al., 2015) and cervical (Bokström et al., 1997, Sakamoto et al., 2005, Yellon et al., 2008, Timmons et al., 2009, Payne et al., 2012, Myers, 2012) tissues as part of the inflammatory response required for parturition to occur, although the requirement of macrophages for cervical ripening is still controversial (Word et al., 2005, Timmons and Mahendroo, 2006, Gonzalez et al., 2009, Gonzalez et al., 2011a). Indeed, we have documented that women who undergo labor at term have increased proportions of pro-inflammatory M1-like macrophages in the decidua compared to term deliveries without labor (Xu et al., 2016). Consistently, women who undergo preterm labor display greater numbers of decidual macrophages compared to women delivering at term without labor (Hamilton et al., 2012, Xu et al., 2016), driven by a rise in macrophages presenting an M1-like phenotype (Xu et al., 2016, Gomez-Lopez et al., 2021a). Moreover, macrophage numbers are increased in human uterine tissues during preterm labor (Xu et al., 2016, Gomez-Lopez et al., 2021a) as well as in the cervix of mice undergoing LPS-induced preterm birth (Timmons et al., 2009, Gonzalez et al., 2011b, Gomez-Lopez et al., 2020). Together, the above studies demonstrate that macrophages in the uterine decidua are polarized towards a pro-inflammatory phenotype as part of the processes of term and preterm labor (Fig. 2B).

Potential macrophage-related interventions for preterm labor—Currently, multiple anti-inflammatory therapies have been tested to prevent preterm labor caused by inflammation (Wakabayashi et al., 2013, Sykes et al., 2014, Xu et al., 2016, Chin et al., 2016, Kadam et al., 2017, Garcia-Flores et al., 2018, Gomez-Lopez et al., 2019c). Given the demonstrated importance of macrophage polarization for pregnancy outcomes, we showed that rosiglitazone can be used to treat LPS-induced preterm birth by activating the PPARγ pathway, thereby reducing decidual macrophage-mediated inflammation (Xu et al., 2016). However, we reasoned that the adoptive transfer of M2-polarized macrophages may represent a more direct approach. The *in vitro* generation of M2-polarized macrophages have been studied and applied as therapeutic treatments in cancer (Andreesen et al., 1998), diabetes (Parsa et al., 2012), neuropathic pain (Pannell et al., 2016), and other inflammatory diseases (Wang et al., 2007, Weber et al., 2007, Hunter et al., 2010), with minimal adverse effects being reported (Andreesen et al., 1998). Investigations in which the transferred M2 macrophages were tracked suggested that these cells will preferentially target inflamed tissues, such as the pancreas in diabetic mice (Parsa et al., 2012). Moreover, the intrathecal administration of M2 macrophages yielded a significant neurological improvement in human patients undergoing treatment for stroke (Chernykh et al., 2016). Such clinical and animal studies, together with current knowledge of the important role for macrophages throughout gestation, hinted that this strategy could be useful during pregnancy. Accordingly, we recently demonstrated that adoptively transferring macrophages polarized to an M2-like phenotype *in vitro* prevented preterm birth and, more importantly, improved neonatal outcomes in a model of LPS-induced intra-amniotic inflammation (Gomez-Lopez et al., 2021a). Such outcomes point to the potential viability of M2-polarized macrophages as a treatment option for women at risk for delivering preterm. It is worth mentioning that such a treatment would not be suitable for all cases of spontaneous preterm labor. Indeed, as described above, administering an antibiotic regimen is considered the optimal approach for treating spontaneous preterm labor associated with intra-amniotic infection (Yudin et al.,

2009, Lee et al., 2016b, Yoon et al., 2019). Thus, the adoptive transfer of M2-polarized macrophages could represent a treatment option for sterile intra-amniotic inflammation; yet, further research is required to demonstrate the feasibility of such an approach.

Conclusion

In summary, here we have provided an overview of the immune mechanisms implicated in intra-amniotic inflammation, the best-characterized cause of preterm labor and birth. While the inflammatory processes driven by microbes (infection) or alarmins (sterile) have some overlap in their participating cellular and molecular processes, the distinct natures of these two conditions necessitate the implementation of specific approaches to prevent adverse pregnancy and neonatal outcomes (Fig. 1A&B). Intra-amniotic infection can be treated using the right antibiotics, whereas sterile intra-amniotic inflammation could be potentially treated using a combination of anti-inflammatory drugs (e.g., betamethasone, inflammasome inhibitors, etc.). Importantly, we have also described the current evidence supporting fetal T-cell activation as a newly described trigger for preterm labor and birth in a subset of cases (Fig. 1C). These findings represent an exciting area of future research focused on further elucidating the fetal immune mechanisms implicated in such a response. Recently, we also provided evidence of two potential immune mechanisms responsible for a subset of preterm births formerly considered to be idiopathic. In the first, we have shown that the impairment of maternal Tregs leads to preterm birth, likely due to the loss of immunosuppressive activity resulting in unleashed effector T-cell responses (Fig. 2A). Second, we have demonstrated the importance of homeostatic macrophages for maintaining pregnancy and promoting fetal development as well as the effectiveness of the adoptive transfer of M2-polarized macrophages for preventing inflammation-induced preterm birth (Fig. 2B). Collectively, in this review, we have discussed established and novel immune mechanisms responsible for preterm birth and highlighted potential targets for novel strategies aimed at preventing the multi-etiological syndrome of preterm labor.

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KEY POINTS

- Intra-amniotic inflammation, driven by microbes ascending from the lower genital tract (intra-amniotic infection) or by alarmins (i.e. danger signals) released upon cellular stress or damage (sterile intra-amniotic inflammation), is the best-established causal link to preterm labor and birth. While intra-amniotic infection can be treated using the correct antibiotic regimen, sterile intra-amniotic inflammation currently lacks approved treatment. Yet, ongoing investigations have identified several promising approaches that could be used to treat women with this clinical condition.
- Pregnancy involves unique mechanisms of maternal-fetal tolerance. Recent investigations have expanded this concept by showing that fetal T cells respond to maternal antigens and are implicated in premature onset of labor leading to preterm birth.
- Maternal-fetal tolerance includes several mechanisms that regulate maternal T cells, including the induction of an exhausted or senescent state, silencing of T-cell chemoattractant expression at the maternal-fetal interface, and the expansion of regulatory T cells (Tregs). A breakdown of such maternal-fetal tolerance, either through the aberrant activation of effector T cells or the impaired functionality of Tregs, can result in preterm labor and birth.
- Macrophages represent a critical cellular component of the maternal-fetal interface. Such cells exert anti-inflammatory functions to promote maternal-fetal homeostasis until term, when they acquire a pro-inflammatory phenotype to promote labor. The importance of macrophages was further established by showing that the impairment of these cells during pregnancy results in preterm labor and birth. Importantly, homeostatic macrophages may represent a viable cellular approach to treat sterile intra-amniotic inflammation.

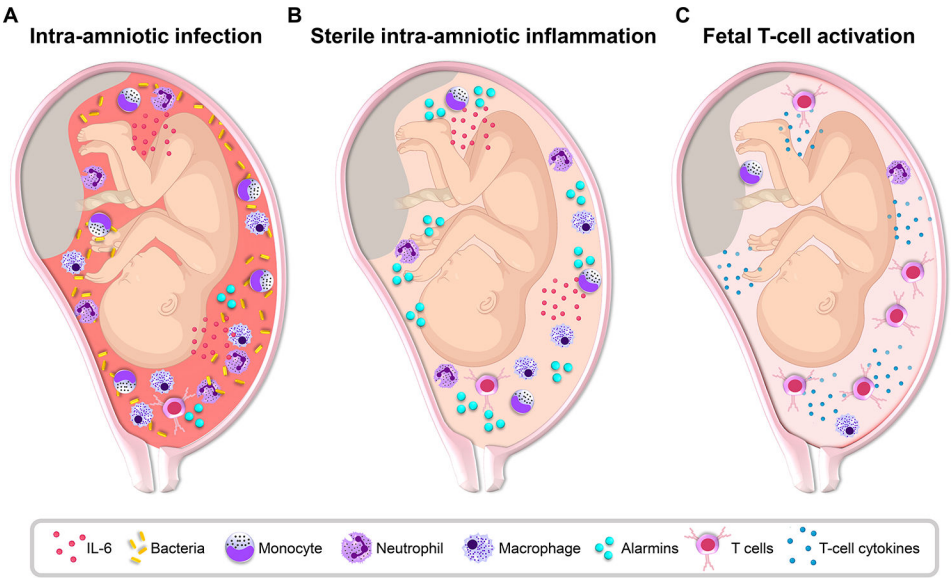

Fig. 1. Distinct immune responses in the amniotic cavity of women with preterm labor.

Representative diagrams of the fetus and amniotic cavity showing the causative agents and responding immune cells associated with distinct immune responses leading to preterm labor. **(A)** Intra-amniotic infection is typically triggered by the ascending invasion of bacteria from lower genital tract and is characterized by a massive local immune response including elevated concentrations of inflammatory mediators such as interleukin (IL)-6 and abundant neutrophils, monocytes/macrophages, and T cells. **(B)** Sterile intra-amniotic inflammation can be triggered by endogenous alarmins and involves elevated concentrations of inflammatory mediators such as IL-6 and a mild infiltration of immune cells such as neutrophils, monocytes/macrophages, and T cells. **(C)** A subset of cases of preterm labor and birth, formerly considered to be idiopathic, can be driven by the fetal immune system, as indicated by the activation and increased presence of fetal T cells and their mediators in the amniotic cavity. This immune response may also include the activation of amniotic fluid resident innate immune cells such as neutrophils and monocytes/macrophages.

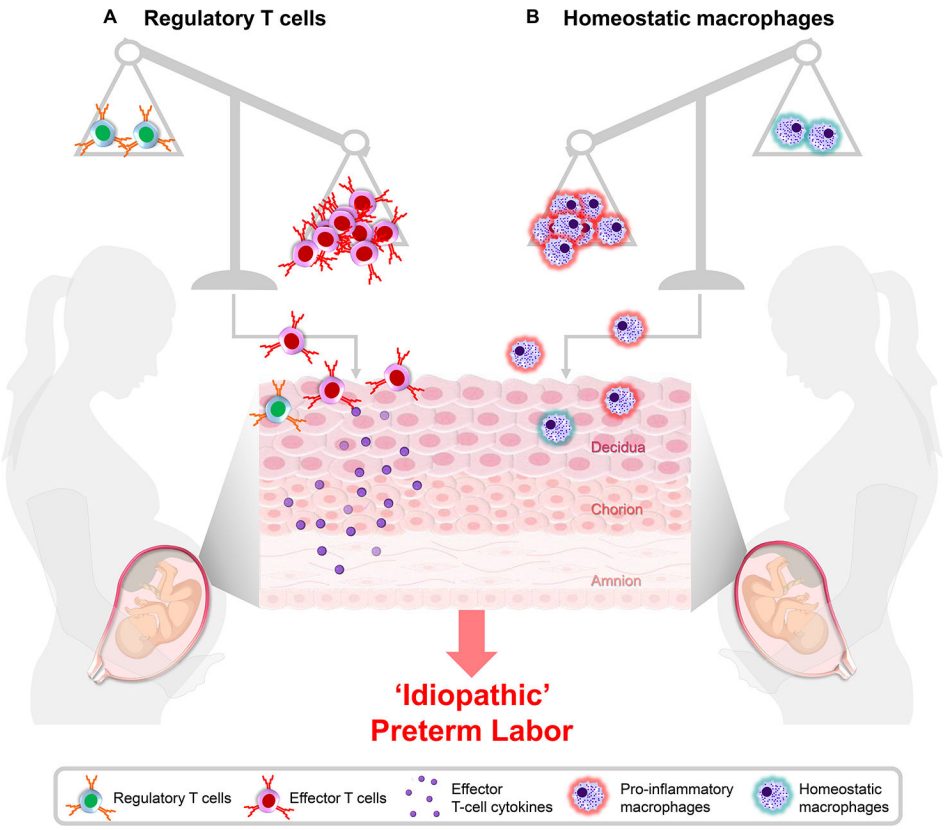

Fig. 2. Regulatory T cells and homeostatic macrophages: two potential mechanisms of 'idiopathic' preterm labor.

(A) Regulatory T cells serve to suppress effector T cells, thereby preventing a maternal anti-fetal immune response. When the balance between regulatory and effector T cells is disrupted, the activation and infiltration of effector T cells at the maternal-fetal interface can occur, leading to preterm labor and birth. **(B)** Homeostatic macrophages are important sentinels of the maternal-fetal interface that act as non-antigen specific mediators of maternal-fetal homeostasis and promote fetal development. The inadequate function of these cells can permit the acquisition of a pro-inflammatory phenotype by decidual macrophages as a consequence of preterm labor, emphasizing the importance of homeostatic macrophages in late pregnancy. Importantly, homeostatic macrophages may represent a therapeutic approach to prevent preterm labor and birth.