the reaction — affects the overall shape of the final molecule[3], which in turn can affect the molecule's function in applications.

Fu and colleagues' advance addresses these challenges. The authors describe a new C–C bond-forming reaction, known as a cross-coupling reaction, that produces one isomer of the reaction product to the near exclusion of the product's mirror-image isomer (in chemists' terms, the reaction is said to be enantioselective). Moreover, the process does not require the use of highly reactive and fragile reagents.

The authors' approach requires three reagents: an alkene, a silane and an alkyl halide (Fig. 1a). Alkenes are not sensitive to air, which distinguishes Fu and colleagues' reactions from the majority of cross-coupling reactions[4], in which the alkene is replaced by an air-sensitive organometallic compound, either as a reagent or as the precursor to a reagent. The new reactions seem to involve an orchestrated set of events wherein the alkene first attaches to a catalytic nickel complex, which is generated *in situ* by a process that involves the silane reagent. The attachment of the alkene produces a transient reactive species, which then reacts with the alkyl halide to form the new C–C bond.

Fu and co-workers' nickel-catalysed process is related to one reported[5] by another team in 2016, but enhances the usefulness of that approach by addressing two key challenges. First, a catalyst had to be identified that not only promotes stereoselective C–C bond formation for an array of different substrates, but also activates the alkene without promoting side reactions between the silane and either the alkyl halide or the alkene. Second, reaction conditions had to be identified that allowed a base to drive catalytic cycles — which is difficult in this context, because bases often interconvert mirror-image isomers.

Not only is the use of alkenes as replacements for reactive organometallic reagents appealing in terms of its practical simplicity, but it also broadens the range of substrates that can be used in Fu and colleagues' reactions. Alkenes are widely available, many are produced industrially on a large scale, and they can be generated by a variety of chemical processes. Alkenes are also especially attractive as reagents for chemical synthesis: they are chemically inert to a range of reagents, but can be induced to react in the presence of the right catalyst and under the right set of conditions. Impressively, the catalytic conditions used by the authors allow alkenes to react without interference when a variety of other common organic groups are also attached to the alkene (see Fig. 2a of the paper[1]).

Intriguingly, when Fu and colleagues used internal alkenes — in which the characteristic carbon–carbon double bond of the alkene is in the middle of a chain of carbon atoms — in their reactions, they observed a phenomenon called chain-walking[6], which causes the double bond to migrate to the end of the carbon chain before reacting. This observation means that products obtained from an increasingly used type of reaction known as olefin cross-metathesis[7] (which produces internal alkenes) might be suitable substrates. It will also be exciting to find out whether the step in which the alkene attaches to the nickel complex can be made to be enantioselective, because this would allow products containing multiple stereogenic centres (carbon atoms to which three different groups are attached by carbon atoms) to be generated enantioselectively.

A particularly notable feature of Fu and co-workers' strategy is that a considerable array of alkyl halides can be used, some of which are not effective substrates for cross-coupling reactions with organometallic reagents. For example, the authors use alkyl halides known as secondary α-halo amides in their reactions, and show that this provides a simple and enantioselective route to prepare compounds that contain a carbonyl (C=O) group next to a stereogenic centre (Fig. 1b). Such compounds are potentially versatile intermediates for chemical synthesis, and have most commonly been prepared using a much less efficient approach based on the use of compounds called chiral auxiliaries[8]. The researchers also demonstrate that they can use their enantioselective reactions to make certain fluorine-containing compounds (see Fig. 1c, for example), which might be useful in medicinal chemistry. Moreover, the chemistry can be used to make compounds that contain quaternary stereocentres (Fig. 1d) — carbon atoms to which four different groups are attached by carbon atoms, which are some of the most difficult structures to prepare enantioselectively.

Overall, this advance is a much-needed method for the enantioselective synthesis of an impressive assortment of versatile small organic molecules, many of which will be of value to research at the frontiers of chemistry. ■

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HUMAN DEVELOPMENT

The landscape of early pregnancy

RNA sequencing of thousands of single cells located at the interface between mother and fetus in early pregnancy reveals remarkable complexity in the cell types and regulatory networks that support reproduction. SEE ARTICLE P.347

SUMATI RAJAGOPALAN & ERIC O. LONG

Scientists have long puzzled over the 'immunological paradox' of pregnancy[1]: how does the mother tolerate the fetus — a foreign entity that carries some of the father's DNA? On page 347, Vento-Tormo *et al.*[2] investigate this enigma. The authors performed single-cell RNA sequencing (scRNAseq) of cells isolated from the placenta and the decidua (the lining of the pregnant uterus), and from matching maternal blood for comparison. They identified an array of cell types unique to this maternal–fetal interface, and inferred the existence of a large network of potential interactions between them that would favour immunological tolerance and nurture the growth of the fetus. The authors' molecular atlas provides an impressive resource for future studies of pregnancy and its complications.

The early embryo develops into a structure called the blastocyst, which implants in the lining of the uterus. Implantation triggers the development of the placenta from fetal membranes. The placenta nourishes the fetus through the umbilical cord[3]. Abnormal placental development can lead to several complications of pregnancy, including pre-eclampsia, fetal growth restriction and stillbirth. A better understanding of human placental development is sorely needed, but there is no good animal model for this process — it has to be studied in women.

Vento-Tormo *et al.* collected placental,

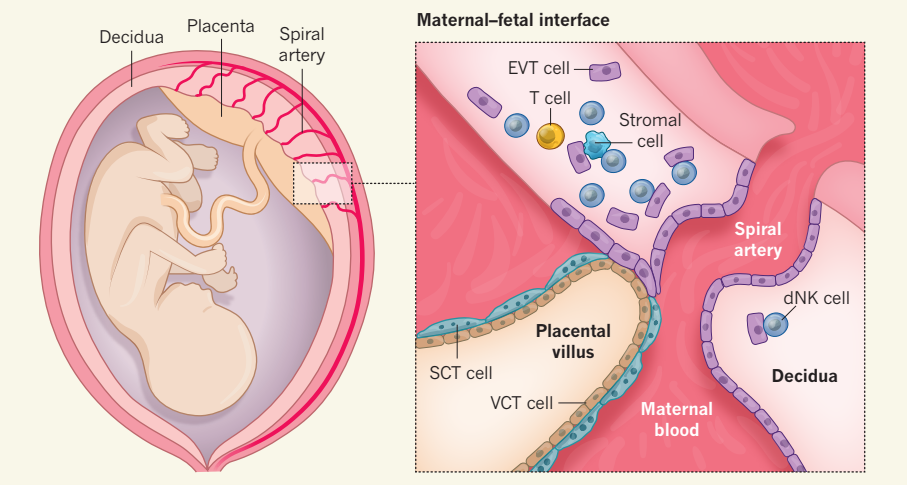

Figure 1 | An atlas of cells at the maternal–fetal interface. During the first trimester of human pregnancy, an interface forms between the maternal decidua (the lining of the pregnant uterus) and the fetal placenta. Nutrients are delivered to the placenta down maternal spiral arteries. Vento-Tormo *et al.*[2] sequenced the RNA of thousands of single cells at this interface, and used the data to define different cell types and to predict interactions between cells on the basis of the receptors and ligand molecules that they express (not shown). The authors' data provide information about fetal cell types derived from the early embryo: villous cytotrophoblast (VCT) cells, which line placental structures called villi; syncytiotrophoblast (SCT) cells that cover the villus surface; and extravillous trophoblast (EVT) cells, which line the maternal blood vessels and intermingle with maternal cells in the decidua. The authors also identified several types of maternal immune cell, including T cells and three subsets of decidual natural killer (dNK) cell, and three types of stromal cell, which provide structural support for the decidua.

decidual and blood samples from pregnancies that had been electively terminated at between 6 and 14 weeks of gestation. The authors' scRNAseq analysis enabled them to distinguish between cells of maternal and fetal origin, because the latter include RNA sequences that are absent in the mother. This clearly revealed that cells from the fetus had migrated into the maternal decidua (Fig. 1), and that a small subset of maternal immune cells called macrophages were located in the placenta.

The blastocyst-stage embryo takes an active role in its own destiny. Cells from the outer layer of the blastocyst, called trophoblast cells, undergo differentiation. Vento-Tormo and colleagues identified the transcription factors involved in the differentiation of one type of trophoblast cell, villous cytotrophoblast (VCT) cells, into either syncytiotrophoblast cells or extravillous trophoblast (EVT) cells (Fig. 1). The authors found that VCT cells express receptors that promote differentiation and are stimulated by growth factors produced by various placental cells. EVT cells invade the decidua, where they interact with maternal white blood cells to trigger the remodelling of narrow maternal spiral arteries into wider conduits that can meet the nutritional needs of the developing fetus. The authors showed that such invading EVT cells produce a signalling protein called transforming growth factor β, which favours the development of maternal regulatory T cells — a subset of immune cells called T cells — that rein in immune responses.

The most abundant maternal immune cells in the decidua during the first trimester of pregnancy are natural killer (NK) cells[4]. Best known as killers of infected cells and tumour cells, NK cells assume a more peaceful role in pregnancy, secreting soluble proteins that promote maternal blood-vessel remodelling[3,5]. Decidual NK (dNK) cells also regulate the extent to which EVT cells can invade the decidua[4]. Vento-Tormo *et al.* identified three subsets of dNK cell — a remarkable finding, because it shows that dNK cells have evolved into specialized cells that are very different from blood NK cells. The authors' data indicate that the immunological activity of each dNK subset is dictated by their ability to interact with both maternal and fetal cells in the decidua, with the dual outcome of promoting fetal growth and restraining immune attack on the fetal cells.

The researchers' work also reveals that the decidua's two layers are defined by distinct molecular profiles, and contain different complements of five cell types: two types of perivascular cell, which support the maternal blood vessels, and three types of decidual stromal (dS) cell, which provide tissues with structural support. The dS cells express the protein interleukin-15, which is essential for NK-cell survival and proliferation, and ligands for two inhibitory receptors on NK cells, indicating the role of dS cells in supporting the survival of NK cells while restraining their immune function.

To analyse their very large data sets, Vento-Tormo *et al.* created a computational platform, CellPhoneDB, to statistically predict receptor–ligand pairs between the different cell types identified by scRNAseq. The platform is publicly available (CellPhoneDB.org) as a resource for examining gene-expression profiles of single cells and for making inferences about networks of cell–cell communication. The authors have highlighted just a few of the cellular interactions revealed by their analysis. Many more remain, and await interrogation.

There are inherent limitations to the study of human reproduction. In this case, samples from pregnancies at 6–14 weeks' gestation were treated as equivalent. But during this time, the fetus is nourished in two distinct ways — first, by glands in the uterus that feed into the intravillous space of the placenta, and, later, by the maternal blood, which passes directly to the developing placenta[6]. Treating these two phases as one might obscure valuable information. Furthermore, changes that occur during earlier stages of embryo development were not examined. Obviously, systematic longitudinal analysis of *in utero* human development is not feasible, because of ethical issues.

A major limitation to understanding human development has been the lack of representative animal models. Vento-Tormo *et al.* now provide a human molecular reference against which pregnancy in animals can be analysed to find features that are shared with humans. In addition, data obtained from women with complications of pregnancy can be assessed using this resource. This could lead to the identification of biomarkers of common pregnancy complications.

By mapping the cellular and molecular terrain of the first trimester of human pregnancy, the current study illuminates how the maternal–fetal interface is a peaceful and tolerant environment in which immunological reactivity is dampened. In such a milieu, maternal and fetal cells cooperate to regulate trophoblast invasion, remodel the maternal vasculature and provide sufficient nourishment for the fetus. However, this immunological tolerance might come at a cost. For instance, the well-known vulnerability to certain infections[7], such as cytomegalovirus, Zika virus and malaria-causing parasites, during this time in pregnancy could be due to restrained immune reactivity. Vento-Tormo and colleagues' data provide a powerful framework in which to assess the landscape of early pregnancy during such devastating infections. ■

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